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Initial OCT4 engagement with the somatic proteome during reprogramming to iPSC

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Declaration

I declare that this thesis is an original report of my research, has been written by me and has not been submitted for any previous degree. The experimental work is almost entirely my own work; the collaborative contributions have been indicated clearly and acknowledged. Due references have been provided on all supporting literatures and resources.

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Abstract

Cellular reprogramming to pluripotency can be achieved by using a defined cocktail of transcription factors, converting differentiated somatic cells into induced pluripotent stem cells (iPSCs). These cells behave like embryonic stem cells (ES) and can be used to generate all cell types in the body. OCT4, SOX2, KLF4 and cMYC (OSKM) were the first set of reprogramming factors defined based on both their importance on maintaining pluripotency, and their ability to reprogram mouse and human somatic cells to iPSCs. Despite recent progress in refining the reprogramming technique, this process is still highly inefficient and often leads to partially reprogrammed cells. This is even more dramatic in human cells, where efficiency is low (∼0.001–1%) hindering the therapeutic prospects and promise of iPSCs and their clinical applications. Extensive studies have been focused in elucidating the molecular mechanisms by which the transcription factors contribute to reprogramming, but there is still a notable lack of understanding of the reprogramming process at the protein level. Particularly little is known about the protein network by which the reprogramming factors maintain pluripotency in human ES and drive pluripotency during the reprogramming process.

Due to the relevance of OCT4 as a core transcription factor for both, the pluripotency network and the reprogramming process, the work present herein focused on studying OCT4 at the proteomic level. By exploiting proteomic approaches focused in on and off-chromatin bound proteins this work described for the first time the OCT4 protein interactors involved in early stages of reprogramming and during pluripotency. For the hES interactome, OCT4 binding partners involved in pluripotency maintenance were identified, in addition to a new set of chromatin associated proteins that have non-previously been described in the pluripotency context. On the other hand, during early reprogramming, OCT4 interactors included somatic transcription factors and other interacting proteins non-previously reported in the reprogramming context, such as proteins involved in cell death, development and differentiation. Further comparison of both interactomes revealed that the initial engagement of OCT4 with the somatic proteome is markedly different from that in ES, illustrating how OCT4 is able to change its chromatin-binding dynamics in order to stablish different phenotypes.

Additionally, the analysis was expanded by applying the same on and off chromatin proteomic approaches to three OCT4 mutants bearing deletions of essential or non-essential reprogramming regions located in the transactivation domains (TAD). This allowed the identification of a unique set of seven proteins present in all the OCT4 with reprogramming capacity (WT or mutant). Interestingly, these were not associated with OCT4 in ES nor the deficient OCT4 mutant bearing a deletion of an essential reprogramming domain. This set of proteins included: UFD1L, RAI1, TNIP2, ETV4, XPO6, FBRSL1 and MCMBP and further functional analysis proved that they are necessary for the reprogramming process as their depletion had negative effects in its efficiency. Remarkably, the biological processes these proteins can be involved are quite varied, including nuclear export, signalling response, post-translational modifications recognition, transcriptional regulation, chromatin remodelling and cell cycle; evidencing the versatility of OCT4 involvement in different processes necessary to achieve the pluripotent state. Furthermore, the mutants' analysis not only allowed the identification of important proteins for reprogramming, but also revealed that removing non-essential reprogramming domains caused more expansive engagement of OCT4 with both the somatic genome and the proteome. These results suggest that different OCT4 regions of the TAD domains contribute to its binding properties, being the essential domains more important for more specific interactions with the genome and more functional interactions with the proteome.

Overall, the findings of this thesis helped to get a better understanding of the protein interactions of OCT4 by describing for the first time the OCT4 networks during reprogramming and pluripotency in human, while revealing that focusing in the properties of the transactivation domains can help understand new biochemical properties of OCT4.

Finally, applying the same proteomic approach analysis to the remaining reprogramming factors, can further help to understand their molecular mechanisms, expand the reprogramming and pluripotency networks, characterize crucial interactors and, thus provide a better understanding of the proteomic molecular mechanisms. This with the ultimate goal of improving the efficiency and fidelity of human iPSCs reprogramming.

Lay Summary

All the parts of our bodies start the same: from a set of special cells. These cells are called embryonic stem cells and they have the potential to become any cell type. Once the cells reach their final fate they are said to be differentiated and lose their potential to become any other cell type. Naturally, in our bodies, these differentiated cells cannot go back to their origins or transform themselves into different cells from another part of the body. However, in research laboratories the story is different, as these cells can be forced to overcome these biological barriers and go back to their origins or change their cell type completely. One of the most interesting conversion process is the one where differentiated cells can go all the way back to be embryonic stem cells again and then become any cell type from there. This process is called reprogramming and it gives origin to cells called induced pluripotent stem cells (iPSC). Even though this mechanism was described more than a decade ago, it is still extremely inefficient, limiting the potential of using iPS in regenerative medicine approaches.

To try to get a better understanding of the process, this work focused in studying interactions happening inside the cells during their way back to stem cells. To achieve this, the original protocol to create iPSCs was used, which involves forcing the cells to express four specific proteins: OCT4, SOX2, KLF4 and cMYC. These four proteins have been described to drive the reprogramming process and stem cells maintenance, but they do not act alone as it has been described that their interactions with other cell components, like DNA and other proteins, are fundamental for their function. Focusing on the protein OCT4, this work aimed to define the proteins that through their interaction with OCT4 are important for the reprogramming process with the final goal of expanding the general knowledge of the process and help its improvement.

Con todo mi cariño para mis personas favoritas:
Papi, Mami, Jonas y Gugus
Saber que siempre han estado junto
a mí ha hecho que todo valga la pena.
Gracias por ser mi motivo para sonreír todos los días.
Esto es por, para y gracias a ustedes.

La culpa no fue de ella,
ni de dónde estaba,
ni de cómo iba vestida.

A la memoria de Fátima, Ingrid
y cada una de las 10 mujeres
que son asesinadas a diario en México.

In memory of Fátima, Ingrid
And each of the 10 women
murdered in Mexico every day.

¡NI UNA MÁS!
NOT ONE MORE!

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List of figures and tables

Abbreviations

DBD	DNA binding domain
DSG	Disuccinimidyl glutarate
EC	Embryonic carcinoma stem cell
EG	Embryonic Germ Cells
EpiSCs	Epiblast stem cells
FA	Formaldehyde
FASP	Fast and Secure Protocol
FBRSL1	Fibrosin Like 1
FDR	False Discovery Rate
FGF	Fibroblast growth factors
GO	Gene Ontology
GSC	Spermatogonial germ stem cells
H3	Histone 3
hES	Human embryonic stem cells
HF	Human Fibroblasts
ICM	Inner Cell Mass
IDR	Intrinsically disordered regions
IC	Immunocytochemistry
IP	Immunoprecipitation
iPSCs	Induced pluripotent stem cells
IVF	In vitro fertilization
K	KLF4
KO	Knock Out
LC-MS	Liquid Chromatography - Mass spectrometry
LIF	Leukaemia inhibitory factor
M	cMYC
MCMBP	Minichromosome Maintenance Complex Binding Protein
MED	Mediator
MEF	Mouse Embryonic Fibroblasts
mESC	Mouse embryonic stem cells
MS	Mass Spectrometry
O	OCT4
OE	Overexpression
OSKM	OCT4, SOX2, KLF4, cMYC
OSN	OCT4, SOX2, NANOG
PCA	Principal Component Analysis
POU-HD	POU homeodomain
POU-S	POU specific
RAI1	Retinoic Acid Induced protein 1
RIME	Rapid immunoprecipitation mass spectrometry of endogenous protein
S	SOX2
SDS-PAGE	Sodium dodecyl sulphate–polyacrylamide gel electrophoresis
SILAC	Stable Isotope Labelling by Amino acids in Cell culture
TAD	Transactivation Domains

TF	Transcription Factor
TNFAIP3	Tumour necrosis factor, alpha-induced protein 3
TNIP2	TNFAIP3 Interacting Protein 2
TSS	Transcription Start Site
UFD1L	Ubiquitin fusion degradation protein 1
VitC	Vitamin C
WT	Wildtype
XPO6	Exportin 6
ZNF	Zinc Finger
3XF	3XFLAG

Contents

Chapter 1 INTRODUCTION

1.1 Pluripotency: From development to cell culture

The development of a multicellular organism from a single cell is a remarkable process, owing to the unique cellular plasticity of embryonic cells [1]. This plasticity known as pluripotency emerges from a specific group of cells in the inner cell-mass of the preimplantation embryo, which then differentiate post-implantation to the three embryonic germ layers: mesoderm, ectoderm and endoderm [2]. The pluripotent state is therefore at the root of embryonic development that give rise to all the somatic lineages as well as the germline [3]. Pluripotency is a transient feature during development, which can only be captured in vitro by deriving pluripotent stem cells from few early embryonic developmental stages. Interestingly, stem cells derived from this limited time window can all be maintained and propagated indefinitely *in vitro* while maintaining the potential to differentiate to all three embryonic germ layers [2, 4]. The dual capacity of stem cells to self-renew and maintain pluripotency (ability to differentiate) define the hallmarks of pluripotent stem cells cultured *in vitro*, providing a powerful tool for understanding the molecular mechanisms early embryonic development. Furthermore, the pluripotency of stem cells can be exploited for disease modelling, drug discovery, animal engineering and regenerative medicine.

1.2 Derivation of pluripotent stem cells

Pluripotent stem cells can be isolated from multiple sources, including pre- and post-implantation embryos, malignant tumours and germ cells and classified accordingly as embryonic stem cells (ESCs), post implantation epiblast stem cells (EpiSCs), embryonal carcinoma cells (EC) and embryonic germ (EG) cells, respectively [5-10] (Fig 1.1). All these stem cells acquire pluripotent properties as displayed by ESCs once cultured *in vitro*, while featuring differential developmental potentials when assessed by a range functional assays for pluripotency, which include in vitro differentiation, teratoma formation, chimaera formation, germline transmission, tetraploid complementation and single-cell chimaera formation [1]. The lowest hurdle for establishing pluripotency consists on the in vitro differentiation to derivates of all three embryonic germ layers where culture conditions that maintain pluripotency are replaced by media specific to

the target tissue, being this approach limited by the availability and efficiency of the differentiation protocols [11, 12]. *In vivo* assays are taken as more robust indicators of potency. The teratoma formation is the standard *in vivo* approach, with assays the spontaneous generation of differentiated tissues from the three germ layers after the injection of the cells to asses in immunocompromised mice. Disadvantage of this assay is that the histological analysis is not capable of asses every single cell type, as well as possible misinterpretation of masses originated by co-injection of matrices or scaffolds, necessitating the use of lineage tracing or markers to distinguish donor cells against host tissue [13]. Blastocyst chimaera formation consists of another in vivo assay, measuring the capacity of pluripotent cells to re-enter development into host embryos in two possible pre-implantation stages: aggregation with morulae or injection into blastocyst, supporting normal development and contribution in all embryonic tissues and germ line. The quality and origin of the stem cell to asses defines the level of chimaeras and embryo viability [14]. Once the chimaera formation is assessed, another robust indicator of the capacity of functional pluripotency is the capacity of test cells to generate functional gametes, defined by the integration of donor cells into the germline transmission, indicating robust chromosomal integrity and functional pluripotency [15]. Tetraploid complementation is used to measure the capacity of the cells to drive the development of an entire organism. Cells to be tested are introduced intro tetraploid host blastocyst, which cannot sustain normal embryonic development, therefore the embryos are derive entirely from the tested stem cell [16]. The most stringent assay involves the injection of single-donor cells into a morula or blastocyst for the generation of chimaeras with widespread contribution from a single cell. As genuine pluripotency is a property of single cells, these chimaeras provide clonal analysis [17]. Despite single cell and tetraploid complementation suffer higher failure rates, depending on the origin and quality of the cell to be tested; they are interpreted as the most definite ways of demonstrating pluripotency in the mouse context, as they are ethically impermissible for human approaches [1].

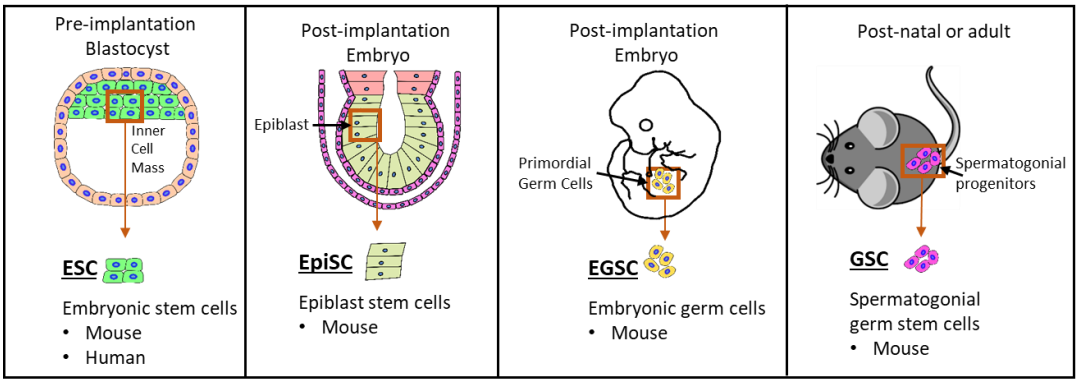


Fig. 1.1 Diversity of pluripotent stem cells. Human and Mouse Embryonic stem cells (ESC) are derived from the Inner Cell Mass (ICM) of the Pre-implantation Blastocyst. Mouse Epiblast stem cells (EpiSCs) are derived from the epiblast of Post-Implantation Embryos. Mouse Embryonic Germ Cells (EGSC) are derived from Primordial Germ Cells from post-implantation Embryos. Mouse Spermatogonial germ stem cells are derived from spermatogonial progenitors from post-natal or adult mice. The diagram was adapted from [4].

1.2.1 Embryonal Carcinoma Cells

The first characterization of the pluripotency capacity of a cell was defined when investigating mouse testicular teratocarcinomas, a form of malignant germ cell tumour. In 1954, Stevens and Little observed that these type of tumours contained a mixture of differentiated cells from all of the three germ layers [18]. When single cells from these tumours were transplanted to a secondary mouse donor, they were able to induce the formation of tumours containing cells from all three germ layers [19]. This particular observation lead to hypothesise that the tumours contained undifferentiated components that were able to give rise to the complex cell mixture of the tumours. Because of their pluripotency potential and the resemblance of the tumours to the embryonic tissue, these cells were called embryonal carcinoma cells (EC) [20]. Further experiments allowed the successful isolation of EC and their propagation *in vitro*. Moreover, the cultured EC cells were able to maintain their ability of multilineage differentiation and develop teratocarcinomas when injected in immune compromised mice. More interestingly, when injected in pre-implantation embryos (blastocyst) certain EC cell lines were able to form chimeras when injected into blastocyst [21, 22]. This evidence indicated that of the pluripotency of EC cells is functionally distinct from its malignant transformation as these cells could lose their malignancy and become benign

without losing pluripotency by contributing to the generation of chimeric animals [23, 24]. Altogether, these observations served as the first platform to define pluripotency *in vitro*, setting the ground for the subsequent isolation of pluripotent stem cells from the mouse embryos.

1.2.2 Mouse embryonic stem cells

The cutting-edge definition and characterization of EC was soon followed by the isolation of pluripotent stem cells directly from mouse embryos. In 1981 two papers reported the first isolation of mouse ES cells. Evans and Kaufman, as well as Gail Martin, were able to sustain the inner cell mass (ICM) of mouse blastocysts on a petri dish, recapitulating early development in vitro and giving origin to the term mouse embryonic stem (mESC) cells (Fig. 1.1) [7, 10]. Since these discoveries, mESC cells have been widely derived directly from the inner cell mass (ICM) of preimplantation blastocysts while maintaining the hallmarks of pluripotent cells of unlimited self-renewal and the capacity to differentiate and give rise to all cells from the three germ layers *in vivo* and *in vitro* [25]. Contrarily to the malignant teratocarcinomas generated by EC, mESC form benign teratomas when injected into immune-compromised syngeneic mice, and are competent at contributing to the three germ layers [26]. Furthermore, mESCs can recapitulate full developmental potential when injected into mouse blastocyst contributing to the formation of high percentage chimeras, a property not frequently seen with certain EC cells. In these chimeras, mESC were also able to contribute to the germline, as it was observed that progeny of chimeric mice crossed with phenotypically distinct wildtype mice were bearing coat pigmentation characteristic of the isolated mESC [27]. More importantly, mESC were able to form a whole embryo when tested in tetraploid complementation assays [14, 16]. Originally, mESC cells were cultured on a feeder layer of mitotically arrested embryonic fibroblasts in a medium containing carefully selected foetal calf serum (FCS). Supplementing this medium with the cytokine leukaemia inhibitory factor (LIF) can maintain the self-renewing state of mESC without a feeder layer by activating Stat3 pathways and the transcription of pluripotency factors [28] [29] (Fig. 1.2). Furthermore, the addition of bone morphogenetic protein (BMP4) proved substitute for FCS and support mESC in combination with LIF via the activation of Smad proteins, resulting in the expression of inhibitors of differentiation [30]. However, under these

culture conditions mESC are morphologically heterogeneous and show fluctuating expression of key pluripotency transcription factors (TF) such as Nanog, which can be solved by inhibiting the mitogen activated protein kinase (Erk) and glycogen synthase kinase 3 (GSK3) (2i), respectively [31]. Under these conditions the inhibition of the FGF4-mediated differentiation pathway perpetuate the pluripotent state and mESC appear morphologically and molecularly homogeneous allowing the robust propagation of mESC cultures with concomitant maintenance of pluripotency [32] (Fig. 1.2). Since these pioneering studies, the 2i+LIF culture system has been stablished to supports more efficient derivation and clonal expansion of mESCs from diverse mouse strains [33, 34] allowing the better characterization of the molecular basis of pluripotency (Figure 1.2). Moreover, the study and characterization of mESC helped to establish the standards to define pluripotent stem cell lines, which include normal karyotype maintenance, immortality and indefinite propagation (self-renewal), and pluripotent capacity (pluripotency assays mentioned in section 1.2) [35].

1.2.3 Human Embryonic Stem Cells

The ability to isolate and culture embryonic stem cells from the ICM was also achieved in humans by Thomson and co-workers, which was first reported in 1998. In this report, the human pluripotent cells were isolated from ICM of donated ex-utero embryos originally produced for *in vitro* fertilization (IVF) and cultured in feeder cells (Fig. 1.1)[36]. The characteristics of these derived hES cells were consistent with the previously identified features in mESC cells: they were capable of long-term self-renewal and indefinite expansion while maintaining a normal and stable karyotype. Additionally, they were able to form benign tumours in immunodefficient mice, reminiscent of the spontaneous human teratomas, which contained endodermal, mesodermal and ectodermal cell derivatives, representing the three germ layers [37, 38]. Due to ethical constraints regarding the generation of chimeric embryos, teratoma assays remain the gold standards of measuring pluripotency of hES *in vivo*. However, *in vitro* differentiation to all lineages have confirmed the pluripotency of hES, providing an essential tool to understand the human development and human diseases and their main differences with mouse [39]. For instance, the maintenance of self-renewal and pluripotency in hES involves different signalling pathways from those in mESC, as LIF is dispensable for hES

and the presence of BMP4 in culture medium induces hES differentiation [40-42]. Factors playing a role in maintaining hES self-renewal include Activin A /Nodal, FGF2. Activin A and Nodal are members of the transforming growth factor (TGF-β) superfamily promoting NANOG and other pluripotency genes transcription via SMAD2/3 signalling. FGF2 signalling also helps sustain NANOG and pluripotency-associated genes expression via the pathways involved in self-renewal and pluripotency such as PI3K/Akt, MAPK/ERK, and Wnt, as well as sustaining expression of pluripotency-associated genes [43-45]. While the derivation of many hES have in principle followed the original methods and conditions previously described, great advances have been made towards improving the culture conditions for research-grade hES, such as stablishing feeder-free conditions with the substitution of cell feeders with coating agents (i.e. laminin), allowing the establishment of clinical-grade hES and stem cell banks (Figure 1.2) [46].

1.2.4 Epiblast stem cells

In 2007, two papers reported the isolation of stable cell lines from the post-implantation epiblast. Brons *et al.* and Tesar *et al.* derived stem cells from a single layer of epithelial cells, which originates from the ICM after implantation in mouse (Fig. 1.1) [5, 9]. These epiblast stem cells (EpiSCs) provided a robust and developmentally-relevant system to study the detailed molecular and cellular mechanisms that function to transition pluripotent cells to their differentiated derivatives [5, 9, 47]. EpiSCs are considered as pluripotent following the criteria of self-renewal and the capacity of multilineage differentiation. Yet, these cells display a limited developmental potential when compared to mESC, as the efficiency by which EpiSCs contribute to chimeras is extremely low and they do not contribute to the germ-line [5, 9, 48]. The limited pluripotency of EpiSCs therefore reflects the advanced developmental stage of the post-implantation epiblast from which these cells originated, in contrast to the more primitive developmental stage of the pre-implantation blastocysts where mESCs were derived from [9, 49, 50]. Additionally mEpiSCs rely on different culture conditions as they are unresponsive to LIF and rely on similar growth factors necessary for hES culture, such as FGF and TGFB/Activin (Fig. 1.2) [9].

1.2.5 Germ Cell lines

Another type of pluripotent stem cells are derived from the germline lineage known as primordial germ cells, which are localized in a specific part of the early post-implantation embryo that will eventually migrate to gonads and give rise to the germ cells [25]. When cultured in vitro, these cells acquire ES-like features and termed embryonic germ cells (EG) (Fig. 1.1) [51, 52]. Pluripotency of EG cells has been confirmed by their capability to generate teratomas and contribute to chimeras [53, 54]. Spermatogonial stem cells from new-born and adult male gonads also generate ES-like cells, although at very low efficiency (Fig. 1.1) [55]. Adult germline stem cells have also been derived from human foetuses, but their characteristics are not as well defined [56].

1.3 States of Pluripotency: Naïve and Primed Pluripotent Stem Cells

The isolation and characterization of mouse pluripotent cells have allowed the identification of two distinct pluripotent states, depending on the developmental stage of their isolation and their growth control conditions: the ground or naïve state, exemplified by the mESCs and the primed pluripotent state represented by mEpiSCs (Fig. 1.2) [57]. The naïve state reflects the unbiased developmental potential of pre-implantation; however, as post-implantation proceeds stimuli trigger the conversion of the naïve cells into a more primed phase that is determined to initiate the lineage-specific programs, where cells start to acquire epigenetic restrictions [58]. Main differences between the naïve and primed states include differences in colony morphologies, better survival rates of naïve cells when passaged as single cells accompanied by shorter doubling time, and different metabolisms for respiration and generating energy [57]. Moreover, the key molecular differences between both cells include differences in their gene expression pattern and epigenetic states, which are more related to the ICM form naïve and early germ layers form primed cells [9]. For instance, in naïve mESC, both X chromosomes are active while primed have already underwent the X chromosome inactivation. Additional epigenetic differences include global DNA hypomethylation (Naïve pluripotency is associated with global DNA hypomethylation) and reduced prevalence of the repressive histone mark H3K27me3 at promoters [59]. Transcriptionally, EpiSCs demonstrate heterogeneous expression of early lineage-commitment markers such as homeobox protein OTX2, Brachyury and zinc-finger protein

ZIC2, indicating early exit from pluripotency [9]. Differences in culture conditions play an important role in maintaining these two distinct pluripotent states. In mouse, naïve conditions can be maintained in two conditions: a more naïve "ground" state in 2i+LIF and a less naïve state in LIF/FCS conditions. In contrast, mEpiSCs, which represent primed pluripotency, are more heterogeneous and display very low clonogenicity [60, 61]. These cells are also unresponsive to LIF and rely on different growth factors, fibroblast growth factor (FGF) and the transforming growth factor beta signalling pathway TGFb/activing (Figure 1.2) [44, 62].

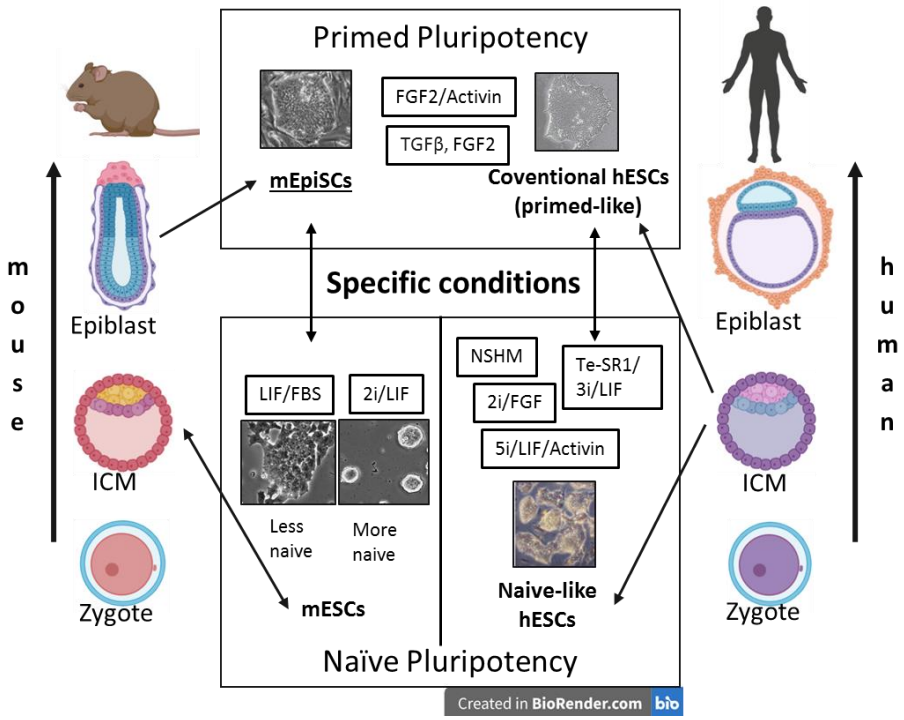


Fig. 1.2 States of pluripotency: Naïve and Primed pluripotent stem cells. Schematic representation of culture conditions (rectangles) used to obtain primed and naïve pluripotent stem cells in mouse and human. In mouse, ESCs and EpiSCs are characterized by a different pluripotent state, called naïve and primed, respectively, which reflects their embryonic origin. The stability and homogeneity of mESCs cultured in 2i+LIF represent a developmental ground state closely reflective that of the ICM of preimplantation blastocysts, in contrast with the heterogeneity of mESCs cultured in LIF +FBS conditions, representing a less naïve state. In human, hES derived from ICM resemble the primed pluripotent state of mEpiSCs derived from the epiblast. Both cell types are dependent on FGF2/Activin/Nodal signalling and grown in similar conditions. hES with mESC-like characteristics can be produced by defined conditions and culture media (rectangles) allowing derivation of naïve hES from either already established primed hES or directly from blastocysts. Image adapted from [4, 63]

Transcriptional and epigenetic characterization of human ESCs have established that they are more related to primed mEpiSCs than to naïve mESC [64]. Although pluripotent, when first isolated, hES were clearly different from mESC cells in their characteristics and culture conditions. Human ESCs were derived from blastocyst using the culture conditions more similar to mEpiSCs, requiring the addition of TGFB/Activin and FGF2, while being insensitive to LIF to culture conditions stablished for naïve mESC (Figure 1.2) [44, 64]. Additionally, hES share many other primed pluripotency properties including low levels of naïve pluripotency markers like KLF17, DPPA3, and lack of restriction H3K27me3 modification over developmental genes, lack of global hypomethylation, and lack of a pre-X inactivation state in most conventional female lines [65, 66]. Regardless of the similarities mentioned above, hES are not identical to mEpiSCs and are considered less primed. For instance, hES do not upregulate the expression of the mEpiSCs marker FGF5 or N-cadherin and has higher expression of some naïve pluripotency markers such as NANOG, REX1 and PRDMD14, which are crucial to maintain conventional hES, as NANOG and PRMD14 depletion induces differentiation [65, 67]. Multiple efforts have been trying to address the derivation of human and other species pluripotent stem cells that resemble naïve mESC with promising successful outputs, suggesting that the naïve-like pluripotent state might be an early developmental stage that is conserved across mammals (Figure 1.2) [57].

1.4 Molecular and transcriptional hallmarks of pluripotency

Regardless of species or pluripotency state, embryonic stem cells are characterized by the expression of an extended pluripotency gene network that sustain self-renewal and suppress differentiation [1]. This is largely governed by the core pluripotency network of set of transcription factors, OCT4, SOX2 and NANOG, collectively known as OSN [68-70].

During mouse development, OCT4 expression is required to maintain the pluripotent cell population of the ICM and epiblast [71]. Carefully balanced OCT4 levels are required for the maintenance of the pluripotent state in vitro. Inactivation of OCT4 in mESCs causes rapid loss of self-renewal and induction of trophoblast (TE) differentiation, whereas OCT4 overexpression triggers differentiation into endoderm (EN) and mesoderm (ME) [72, 73]. In hES, low levels of OCT4 can induce ectoderm or extraembryonic differentiation, while

high levels can promote self-renewal or specify mesendoderm lineages [74]. NANOG is also an important factor in early mouse development. Although required at a later point than OCT4, NANOG is restricted to the ICM and epiblast of the early embryo controlling the epiblast versus primitive endoderm (pEN) decision in the blastocyst [75]. Different levels of Nanog *in vitro* also revealed its important role in mESC self-renewal, as Nanog depletion causes these cells to differentiate into a broader repertoire of cell lineages, primarily TE and pEN lineage [72]. Moreover, NANOG overexpression enables mESC to self-renew independently of LIF [76]. In hES, NANOG is involved in repressing embryonic ectoderm differentiation, but has no effect in other lineages. Lastly, SOX2 is expressed in the pluripotent lineage of the mouse embryo and is required for epiblast maintenance [77]. Sox2-depleted mESCs differentiate primarily into TE in vitro. Whereas, SOX2 is involved in repressing mesendoderm differentiation in hES [72, 74].

OSN are members of different structural families of transcription factors. OCT4 is member of POU family, NANOG is a member of the homeobox family and SOX2 is member of the SRY-related HMG-box (SOX) family. Because of their ability to bind specific DNA sequences, OSN are known to target genes that maintain pluripotency. Studies focused in mESCs a hES have reported the genome-wide binding patterns of OSN, showing that OSN occupy the promoters and enhancers of pluripotency genes including their own genes [68, 78]. Moreover, these reports showed that OSN co-occupy and regulate two type of genes to co-ordinately regulate their transcription. The first set of genes encode important genes that promote self-renewal and include transcription factors (e.g. STAT3, ZIC3), signal transduction components (e.g. TGDF1, LEFTY) and chromatin modifying enzymes (e.g. SMARCAD1, MYST3), among others. The second set of genes targeted by OSN are silent in ES cells but remains poised for subsequent expression during cellular differentiation [68, 78, 79]. These genes include a set of transcription factors which expression results in lineage commitment and differentiation (e.g. NEUROG1, PAX6, and OTX1). The coordinated and efficient repression of these genes is essential to help maintain the undifferentiated state of the pluripotent cells [68, 78]. Characterizing the chromatin state of the promoters of these poised genes revealed a bivalent enrichment for histone post-translational modifications consisting of both the repressive histone H3K27me3 and the activating histone H3K4me3. Interestingly, most

of these bivalent domains were also co-occupied by the epigenetic repressor proteins Polycomb group (PcG) proteins and by the RNA polymerase II (POLII), explaining how these genes encoding developmental regulators existed in a poised state, meaning repressed in pluripotency, but ready to be expressed upon differentiation [78, 80, 81]. Moreover, given that the proteins rarely act alone, one approach towards the understanding of this molecular mechanism is to look at its protein interaction level. From integrated mouse dataset based in the OSN protein interactomes, Sall4, Tcfcp2l1, Dax1, Esrrb, Rex1, Nac1 and Zfp281 were identified as part of the pluripotency network. Furthermore, interactomes using these proteins as baits have been analysed to gain a more complete view of the pluripotency protein interaction network [82]. Integration of these proteomics datasets gave a network comprising 239 proteins, being transcription factors one of the overrepresented groups [83]. The nucleosome remodelling histone deacetylase (NuRD) complex was among the most prominent complex identified in the embryonic stem cell protein-interaction network suggesting that the transcription factors co-recruit the same machinery, NuRD for histone deacetylation as a gene repression mechanism to regulate pluripotency. Besides NuRD, other complexes involved in chromosome remodelling and part of the basic transcriptional machinery have been reported [84-87]. Overall, as data accumulation continues towards a more complete embryonic stem cell protein interaction network (discussed in section 1.6.3), the physical protein-protein interaction (PPI) networks of pluripotency factors including OSN and other proteins have provided valuable information of a well-coordinated and multi component process, linking transcription to chromatin and signal-transduction pathways that are required to maintain pluripotency.

1.5 Reprogramming somatic cells towards pluripotency

The isolation of pluripotent cells and the definition of the underlying gene regulatory networks that govern pluripotency and differentiation processes have contributed to the derivation of differentiated cell types from pluripotent stem cells. However, the source of pluripotency is restricted to the early embryo, as differentiation is regarded as an irreversible process during development by which cells gradually lose potency. The evidence that differentiated cells can be forcibly reverted back pluripotency was first reported by Professor John Gurdon, who established that by injecting the nuclei of

epithelial cells into enucleated *Xenopus laevis* eggs resulted in the generation of normal tadpoles, which nuclei could be transplanted again into enucleated eggs and develop into fertile adults (Fig. 1.3) [88, 89]. This approach known as somatic cell nuclear transfer (SCNT) was successfully applied in mammals including primates [90-92]. Therefore, somatic cells retain the genetic information necessary to become any other cell type, and that the epigenetic effects of differentiation could be reverted by the presence of adequate factors. Since then, several studies have achieved the conversion of somatic cells to a pluripotent state, such as cell fusion of somatic cells with embryonic stem cells [93, 94]. However, the main limit of these techniques is that they require oocytes and ES cells as the principal driver of cell fate changes (Fig. 1.3). Still, these techniques lead to the hypothesis that there were factors present in pluripotent stem cells and oocytes that can drive cell fate conversion [95].

Taking advantage of the resources available in the literature of the genes involved in the self-renewal and maintenance established thanks to ES cells, Shinya Yamanaka and Kazutoshi Takahashi tested the hypothesis that these genes could be responsible for reverting somatic cells into pluripotency. By taking 24 of these genes and overexpressing them in mouse embryonic fibroblasts (MEF) in ES cell culture conditions they were able to generate what it is known as induced pluripotent stem cell (iPSCs) [96]. From these 24 genes, they could narrow the list to just 4 factors: OCT4 (O), SOX2 (S), KLF4 (K) and c-MYC (M). These four factors included two of the main factors of the pluripotency core network (OS) and were defined as the minimum required factors to induced pluripotency from fibroblasts. In the same report, they probed the ability of these factors, also known as OSKM or Yamanaka factors, to induce pluripotency from adult tail-tip mouse fibroblasts (Fig. 1.3) [96]. Characterization of the first resultant iPSCs showed that they could be propagated using the same culture conditions of mESC, that they were able to reactivate ES cell associated genes an therefore had similar transcription profiles to mESC, presented demethylation profiles in certain pluripotency promoters, contributed to the three germ layers in teratoma formation assays but were not able to produce full adult chimeras after injected in blastocyst in spite contributing to the three germ layers in the chimeric embryos [96].

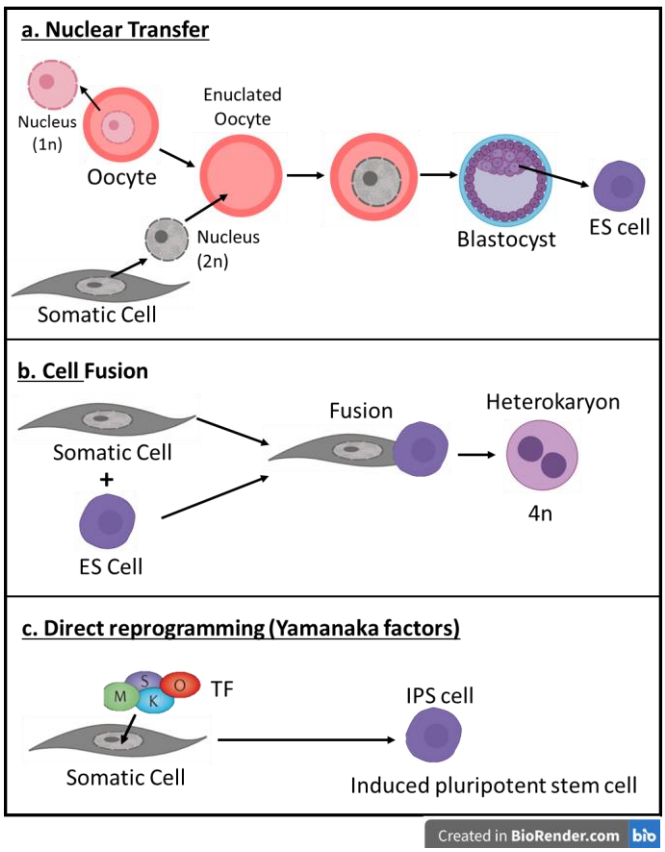


Fig. 1.3 Nuclear reprogramming methods. Approaches for restoring developmental potential to somatic cells. a. Nuclear transfer involves the transplantation of the nucleus of a somatic cell (diploid 2n) into an enucleated oocyte replacing its genetic material (haploid 1n). In the oocyte environment, the somatic cell nucleus is reprogrammed so cells derived from it become pluripotent allowing the development to the blastocyst stage from which embryonic stem cells can be derived for tissue culture. b. Cell fusion requires the hybridization between ES cells and somatic cells to form a single entity, yielding multinucleated heterokaryons (tetraploid 4n) ES cell lines. By altering the nuclear ratio in the fusion, and hence the stoichiometry of the regulators provided by each type of cell, the heterokaryon is reprogrammed towards the desired cell type, influenced by the culture conditions as well. c. Direct reprogramming requires the introduction and expression of defined transcription factors directly to the somatic cell, without requiring ESs or oocytes as starting material. This approach leads to the formation of induced pluripotent stem cell (iPSCs), which have similar properties to ES. OSKM or Yamanaka factors represent the original reprogramming factors. Image adapted from [97].

Further works, however, successfully produced fully reprogrammed iPSCs that could contribute to mouse chimeras and to the germline, demonstrating the pluripotent identity of iPSCs [98, 99]. Since the iPSCs initial discovery, reprogramming to iPSCs has been achieved using different somatic cells of origin. For instance shortly after the mouse

study, the OSKM factors were able to reprogram human adult fibroblasts into hiPSCs and maintained in human ES growing conditions, suggesting that the fundamental transcriptional network defining mouse and human pluripotency involves similar mechanisms while influenced by different signals and growing condition factors [100, 101]. These hiPSCs could be maintained in human ES growing conditions, displaying hES morphology, and had the ability to differentiate into the three germ layers in teratoma assays and embryoid body formation [100, 101].

Following the breakthrough discovery of iPSCs, induction of pluripotency from somatic cells by transcription factors has been a main field of study, revealing the complexity of this long and highly inefficient process, particularly in the human context. [102].

1.5.1 Epigenetic mechanisms of cellular reprogramming to induced pluripotency

The reprogramming of somatic cells into iPSCs is a long and complex process that involves the re-activation of the repressed pluripotency gene and the silencing of somatic genes [103]. Thus, the induction of pluripotency could be regarded as a mechanism where the pluripotency network gradually overcomes the epigenetic landscape that guards the somatic cell identity (Fig. 1.4) [104].

1.5.1.1 Chromatin structure in cellular reprogramming

Pluripotent stems cells have a unique epigenetic landscape that differentiates them from differentiated somatic cells (Fig. 1.4). In pluripotency, the chromatin is in more open or permissive state, enriched with the active histone marker H3K4me3 and hypomethylated DNA around the promoters of the pluripotency genes. On the other hand, during differentiation and lineage commitment the pluripotency genes are silenced and repressed with H3K27me3 and H3K9me3, while DNA gets methylated, resulting in a closed heterochromatin conformation. In addition, the genes responsible for the cell identity of the somatic cell remain active. Therefore, to be able to achieve the pluripotency-like epigenome, chromatin remodelling, histone-post translational modifications resetting, DNA demethylation and reactivation of the silenced X chromosome must be successful [95, 99, 100, 105, 106].

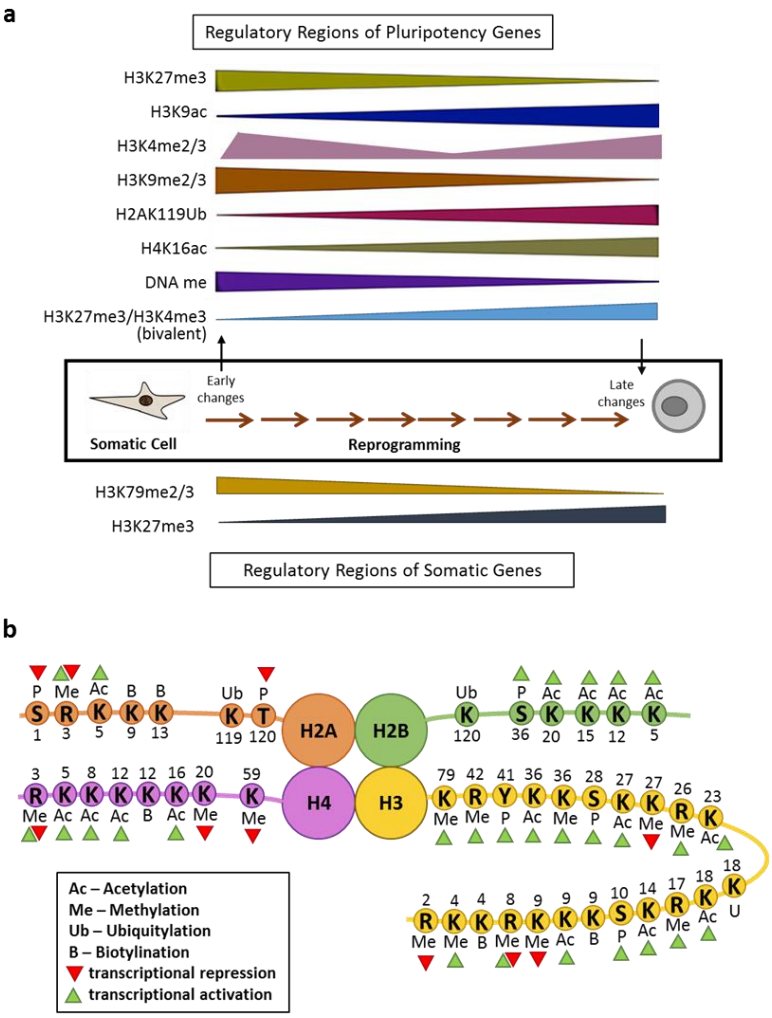


Fig. 1.4 Epigenetic changes of induced pluripotency. Turning on pluripotency genes and turning off genes responsible for the maintenance of a differentiated somatic cell state. a. Epigenetic changes discussed in this thesis during reprogramming in regulatory regions of pluripotency genes (top) and in regulatory regions of somatic genes (bottom). For pluripotency genes, reprogramming leads to acquisition of active histone marks (e.g., H3K9ac, H3K4me) and loss of repressive histone marks (H3K9me and H3K27me) and DNA methylation on pluripotency genes, which facilitates the opening up of a compact chromatin structure and thereby allowing exposure of pluripotency gene promoters and binding of pluripotency factors. In somatic genes, reprogramming leads to removal of active chromatin states in active genes (H3K79me) and the gain of repressive chromatin states (H3K27me). b. Common Mammalian core histone modifications of histones H2A, H2B, H3 and H4. Post-translational covalent modifications include acetylation (Ac), methylation (me), phosphorylation (P) and ubiquitination (Ub). Effects of the modifications in gene regulation are shown as active (green triangle) or repressive (red triangle). Amino acids and positions where the modifications have been reported are indicated.

Changes in chromatin structure, nucleosome composition and histone post-translational modification patterns are involved in the reshaping of the somatic epigenetic landscape during reprogramming [107]. Therefore the initial repressive state of chromatin represents another mechanistic barrier in reprogramming as pluripotency related genes present repressive histone markers such as H3K27 and H3K9 methylation while lacking the active H34Kme3 [108]. One of the key epigenetic blockades to reprogramming associated with histone modifications is the presence of the H3K9 trimethylation, which silence gene expression by promoting the formation of long-range heterochromatin [109].

Genome wide binding profiles of OSKM factors at early stages of human reprogramming revealed that mega base regions enriched with H3K9me3 are inaccessible to the reprogramming factors at early reprogramming, contrary to ES and iPSCs, therefore named differentially bound regions (OSKM-DBR) [110]. The transient knock down of H3K9 methyltransferases SUV39H1/2 enhanced OCT4 and SOX2 binding at the OSKM-DBR regions and increased reprogramming efficiency. [110]. Furthermore, a proteomic approach focused on global quantification of the different histones modifications at different reprogramming stages revealed that pre-iPSCs and MEFs were more enriched for repressive H3K9 methylation marks than iPSCs and corroborated that the H3K9 methyl transferases increases reprogramming and promotes decondensation of chromatin [111]. Agreeing with these observations, knock down of H3K9 demethylases such as KDM3A/B, KDM4A/B inhibit reprogramming, whereas overexpression of KDM4B promotes the conversion of pre-iPSCs to iPSCs [109, 112].

Genome-wide characterization of epigenetic changes that take place within the first cell cycles after the induction of OSKM in MEFs revealed that the ectopic factors initiate a gradual change of chromatin opening by first depositing the H3K4me2 mark, the precursor of the active H3K4me3 mark, at important pluripotency targets, prior to gene activation (Fig. 1.4) [113]. Furthermore, major H3K4me3 changes were identified in intermediate reprogramming stages of MEFs, which is followed by a second wave of changes closer to the pluripotent chromatin state and resulting in gene reactivation [114]. These studies also revealed the initial loss of the repressive H3K27me3 mark in

specific loci [113, 114]. The gradual gain of H3K27me3 together with H3K4me3 has also been reported during the reprogramming process resembling the pluripotency bivalent domains observed in pluripotency maintenance (Fig. 1.4) [114].

Other histone modifications such as H3K36me2/3 and H3K79 methylation have also been associated to facilitate reprogramming. Lang *et al.* described that the overexpression of the H3K36me2/3 demethylase KDMB2 enhances reprogramming by binding to promoter of early activated genes including epithelial and pluripotency genes [115], while Onder *et al.* described that the inhibition of the H3K79 methyltransferase facilitates the loss of this histone mark from somatic genes increasing the reprogramming potential (Fig. 1.4) [116].

The evidence that histone modifications and DNA methylation act as barriers and facilitators of reprogramming has allowed the identification of important chromatin-modifying enzymes and how their modulation influences the reprogramming process. For instance, as widely discussed, reprogramming requires the acquirement of ES permissive euchromatin, which allowed to relate the importance of chromatin remodelers required for ES maintenance with the reprogramming process. For example esBAF (Brm/Brg-associated factor in ES cells) and Ino80 (inositol requiring 80), which are members of the SWI/SNF family of chromatin remodelling factors and are required for the maintenance of ES, also have important roles in reprogramming. In ES esBAF and Ino80 complexes co-localize with the pluripotency factors generating an open chromatin structure and their overexpression along with the reprogramming factors facilitate the binding of the transcription factors to their targets [117, 118]. Additionally, members of the esBAF family target and facilitate the de-methylation of *Pou5f1* and *Nanog* promoter, while down-regulation of Ino80 reduces reprogramming efficiency and results in a more closed chromatin state near pluripotency gene promoters and reduces reprogramming [118, 119]. Similarly, a member of the CHD (Chromodomain helicase DNA binding) family remodelling factor, CHD1 maintains open chromatin in ES and its downregulation results in the accumulation of heterochromatin leading to reduction of reprogramming efficiency [120].

Furthermore, complexes involved in gene repression had also been identified as important for both pluripotency and reprogramming. For instance Mbd3/NuRD (nucleosome remodelling deacetylase), a complex responsible for the deacetylation of histones and required for silencing pluripotency genes during differentiation of the ES cells [121] has been associated to reprogramming but with different outputs. Rais *et al.* and Luo *et al.* reported that depletion of Mbd3 and the associated NuRD component Gatad2b increases reprogramming efficiency, leading to a deterministic synchronised iPSCs generation, favouring the re-activation of pluripotency genes [122-124]. However, another study reported that Mbd3 is necessary for efficient iPS generation from neural stem cells, pre-iPS and EpiSCs [125]. The difference reported could be the result of the different cell context, as different culture conditions and induction methods were used, and further investigation is required to clarify the exact role of Mbd3/NuRD in iPSC generation. Moreover, WDR5, which is a core subunit of the histone methyltransferase complex Set/Mll in charge of active H3K4 methylation, has been shown to be required for efficient methylation of H3K4 in the first wave of histone modifications during early reprogramming [126]. Additionally, WDR5 has been shown to interact promoters enriched for targets of OCT4 and SOX2, which gain H3K4me2, while its depletion has negative effects in reprogramming [126]. Consistently, it was shown that the counterpart enzyme responsible for demethylation of H3K4 acts as a barrier in the process. KDM5B, a member of jumonji C-containing protein complexes, is responsible for demethylation the active histone mark H3K4me1/2/3, a process that can impair reprogramming. In fact, when KDM5B was depleted in the process, it promoted the efficiency, which pairs with the negative effects of WDR5, as erasing the mechanisms to add the active H3K4 methylation markers affects reprogramming, whereas erasing the mechanisms to remove it promotes the formation of iPSCs [127].

As the gain of repressive chromatin states to downregulate somatic genes is important to promote induction of pluripotency, the removal of active histone marks already present in somatic active genes also represents mechanisms involved in downregulate the original somatic transcription profile. This was probed by the inhibition of Dot1L, which establishes the active H3K79me2 and H3K79me3 marks present in gene bodies, significantly enhanced the reprogramming process (Fig. 1.4) [116]. Furthermore, the

early removal of the heterochromatin patterns observed by the loss of the repressive histone mark H3K27me3 is believed to be helped by UTX, a Jmj domain-containing enzyme. When depleted, reprogramming is deficient and global aberrations of H3K27me3 and H3K4me3 profiles are observed when reprogramming MEFs depleted of UTX, abolishing the ability of somatic cells to reach the pluripotency state. Furthermore, despite it has been shown that UTX removes repressive marks from pluripotency genes; its overexpression has no positive effect in iPS formation [128]. More interesting, studies focused on another H3K27me3 demethylase, Jmjd3 (Kdm6b), suggested that the function of these proteins is loci specific, as depletion of Jmjd3 contrarily to UTX improves reprogramming [129].

Despite the somatic pattern of H3K27me3 needs to be erased from repressed genes, gain of this histone modification is also a mechanism used for silencing somatic genes. The complex that has been involved in this mechanism is the Polycomb Repressive Complex 2 (PRC2), which is responsible for the trimethylation of H3K27 [130]. The importance of this complex was described when downregulation of the subunit Eed and therefore the loss of all PCR2 complexes, resulted in severe deficiency of the reprogramming process. Corroborating the fact that silencing through H3K27me3 is an important step, the overexpression of the catalytic subunit Ehzh2 improves the reprogramming efficiency in mouse and human, whereas the absence of other PRC subunits also affected the iPSC generation [131, 132].

1.5.1.2 DNA methylation during reprogramming

DNA methylation in gene promoters is typically associated with a repressed state of gene expression [133]. During differentiation, *de novo* DNA methylation silences key pluripotency genes such as OCT4, SOX2 and NANOG [134]. This mechanism is mediated by the *de novo* methyltransferases DNMT3A and DNMT3B and preserved by the maintenance methyltransferases DNMT1 [66]. During reprogramming, these repressive marks need to be removed in order to allow the transcription or the pluripotent genes [135]. Demethylation process during reprogramming involves downregulation of DNMT1 and therefore progressively diluting DNA methylation during replication and the facilitating the final transition to iPSCs [136]. TET proteins (Ten-eleven translocation

methylcytosine dioxygenase) are responsible for the loss of DNA methylation from the paternal genome during development [137], by mediating the iterative oxidation of 5mC to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) followed by their replication-dependent dilution [138]. TET proteins appear to have a more direct contribution in reprogramming possibly through their activation by the OSKM factors, as after their induction in MEFs, TET2 promotes the hydroxymethylation of key pluripotency genes, such as Esrrb and NANOG, preparing them for subsequent demethylation and activation [139], while TET1 facilitates iPSC induction by promoting Oct4 demethylation and reactivation and is able to replace OCT4 in the reprogramming cocktail [140]. Additionally, the depletion of TET2 has negative effects in the reprogramming, while the overexpression of NANOG and TET1 or TET2 enhances it, possibly as a result of the reported interactions of TET1 and TET2 with NANOG and their co-bind in pluripotency targets in ES [139, 141]. Furthermore, activity of TET proteins can be promoted by the addition of Vitamin C to the reprogramming media, as it can interact with the catalytic domains of TET1 and TET3 and enhance their enzymatic activity, hence the reprogramming process [142]. Despite the improvement of the methylation dynamics during reprogramming has been achieved by the addition of chemicals to the reprogramming media, like VitC, one of the remaining issues to address in the reprogramming process is the result of the inefficient complete demethylation to that one in ES cells [143]. Mbd3, a member of the repressive NURD complex crucial for heterochromatin compaction could be involved in this inefficiency, as it has been shown that in mESC, it associates with loci enriched for TET1 and 5hmC, opening the possibility that in reprogramming it is recruited to these sites preventing the demethylation unless its release by coactivators [123, 144]. On the other hand, *de novo* methylation to supress somatic genes could not be a greater barrier than demethylation, as iPSCs can be generated in the absence of DNMT3A and DNMT3B [145]. Moreover, it has been shown that iPSCs retain an epigenetic memory owing to similar DNA methylation to the somatic cell of origin, which could influence in the differentiation potential of iPSCs to certain lineages, highlighting the importance of the DNA methylation mechanisms for faithful reprogramming to bona fide iPSCs [146, 147]. Taken jointly, chromatin-associated proteins can contribute both positively and negatively to the reprogramming process to iPS.

1.5.2 Inducing pluripotency by the reprogramming factors OCT4, SOX2, KLF4 and c-MYC

One of the key features of transcription factor induced pluripotency is their involvement in the induction of the large-scale chromatin changes that result in the acquisition of the epigenetic landscape of ES. Since the description of the original reprogramming factors OSKM, different TF combinations containing some or none of OSKM have been able to reprogram towards iPSCs, although with lower efficient, mixed reproducibility or the need of more than four factors [148-150]. Additionally, OSKM has been describe to be successful in a wider range of cell types. Most importantly, they are up to now the most used system for the derivation of human iPSCs; therefore, several efforts have been focused in understanding how their induction orchestrates the reprogramming process.

As discussed in the pluripotency section, POU family member OCT4 and homeobox family SRY-related HMG-box family member SOX2 are two of the core factors in the pluripotency network with fundamental roles for development and pluripotency maintenance, so it was not unexpected that they were common requirements for both mouse and human. Moreover, KLF4, a member of the Kruppel-like factor family and c-MYC, a member of the Basic helix-loop-helix family, belong to a set of pluripotency auxiliary TFs. Because of their transcription factor (TF) nature, they have the capacity to bind DNA. In fact, the engagement of OSKM with the pluripotent genome has been characterised, finding that OCT4, SOX2 and KLF4 are more enriched in enhancer regions, opposite to c-MYC, which binds to gene promoters. Moreover, the recruitment and co-binding with additional pluripotency TFs, such as NANOG and ESRRB, in specific loci maintain the transcriptional network of pluripotency. [151-153].

1.5.2.1 OSKM engagement with the somatic genome

Extensive genome-wide chromatin assays, along with transcriptomic and epigenetics analysis from different stages of the reprogramming process had provided insights into the multiple synergistic or unique properties and effects of the OSKM engagement with the genome. Most of the recent studies have focused on characterizing the OSKM early binding to the somatic genome and how this contributes to the repression of somatic genes and the activation of pluripotency genes using both human and mouse models

[110, 154, 155]. The binding of OSKM to the human somatic genome have been mapped 48hrs after OSKM induction in human fibroblast , which is considered as an early stage of reprogramming prior to major transcriptional changes and exposure to ES media [113]. In this study, Soufi *et al.* (2012) reported that OSKM binding profiles were different from those in ES cells [151]. Analysis of the shared binding sites revealed that OSKM extensively co-bind the same target sites. Most interestingly, analysis of the chromatin state of OSKM binding sites revealed that OSK, and not c-MYC preferably bind to DNase-I resistant or inaccessible DNA, acting as pioneer factors (Fig. 1.5) [110].

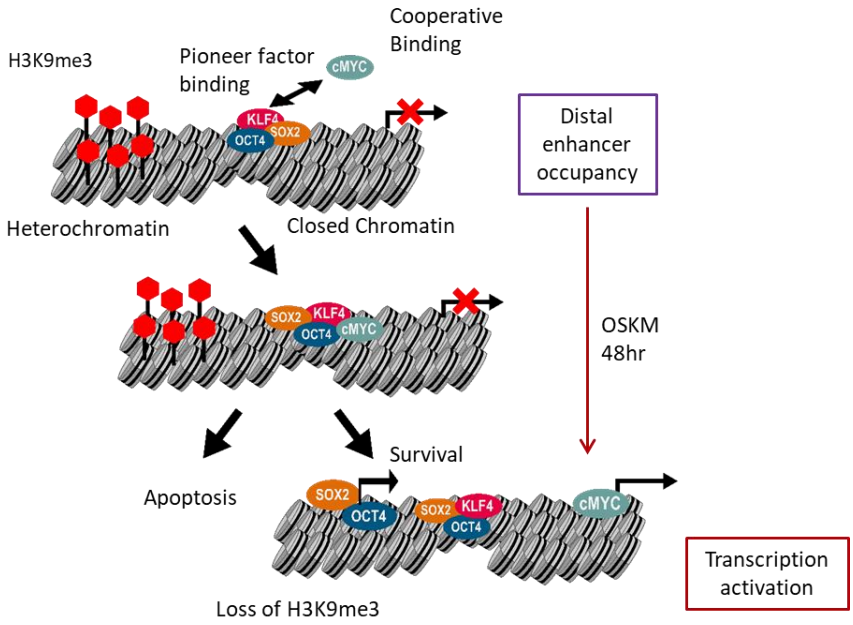


Fig. 1.5 Initial targeting of somatic closed chromatin by pioneer factors OCT4, SOX2 and KLF4 (OSK). OSK target nucleosome DNA in closed, silent at distal enhancer elements. c-MYC facilitates OSK chromatin engagement. Initial engagement enables other factors, chromatin modifiers and remodelers to access the target sites, modify the chromatin landscape and initiate the reprogramming of silent genes, enabling cell type conversion. Mega base-sized heterochromatin domains of the genome that are refractory to the initial OSKM binding are represented by H3K9me3 markers (red hexagons). Cells that achieve the loss of H3K9me3 and transcriptional reactivation are more prone to achieve a more stable reprogramming. Image modified from [110].

Pioneer factors are defined by their ability to occupy DNA targets in closed chromatin, inducing the reshaping of the chromatin to a more open state providing accessibility for other transcription factors and co-factors to bind [156] (Fig. 1.2). Furthermore, Soufi *et*

al. also observed that the closed chromatin binding regions of OSK were localized in regions distal to gene promoters, like enhancers, whereas c-MYC was only able to engage these regions in the presence of OSK [110]. Comparisons of the unique and shared sites for each factor revealed that KLF4 and c-MYC can co-bind to actively transcribed promoters, but combinations with OS were mostly enriched in closed chromatin. Moreover, despite c-MYC was not necessary for OSK to access closed chromatin, it facilitates their binding [110]. Further characterization of the pioneer function of OSK revealed that it relies on the OSK capacity of binding nucleosomes by recognising partial DNA motifs [157].

Differently from what Soufi *et al.* and further reports observed [158, 159], evidence of the initial OKSM engagement with the somatic genome in the mouse context described by Chronis *et al.* suggests an alternative model of the binding and role of the factors in the silencing of somatic genes. This work, which was focused in mouse reprogramming, suggests a model, at 48hrs OCT4, SOX2 and KLF4 preferentially bind co-bind to distal somatic active enhancers, whereas c-MYC engages with gene promoters [154]. In this study, Chronis *et al.* described that early OSK co-binding to active somatic enhancers leads to their inactivation genome wide and silencing of their somatic gene targets. Analysis of the engagement of TF bound to these enhancers such as Runx1, showed a combinatorial binding between OSK and the somatic TF, which could facilitate their redistribution to new sites elsewhere already engaged by OSK, such as transient enhancers or pluripotency associated enhancers. This redistribution leads to the inactivation, gradual loss and silencing of the TF and their target genes. Additionally, the OSK engagement induces the loss of active chromatin marks as a result of HDAC1 binding, which is a histone deacetylase that functions as a co-repressor, and the loss of p300, a histone acetyltransferase that functions as a co-activator, leading to gene repression, thus a negative feedback loop where the somatic genes and the somatic transcription factors get silenced. [154]. This evidence correlated to a study that characterised the early OCT4 binding (no SKM) in MEFs, observing the same pattern of binding permissive/active chromatin that correlated with subsequent somatic gene silencing of bound regions [160]. Moreover, despite not being the preferred binding as observed in Soufi *et al.*, this work defined that pluripotency enhancer selection also begins early

reprogramming involving a stepwise process through collaborative binding of OSK at sites with high OSK-motif density, leading to the activation of pluripotency genes at late stages [154]. Discrepancies between both reports could be due to the lack of information regarding the state of the chromatin pre-OSKM induction in the mouse report, as analysis of chromatin state was focused in 48hrs, where chromatin is already different from MEFs with no OSKM induction. Moreover, a systematic comparison between both data sets confirmed the differences in binding preferences to distinct chromatin states, with little overlap of common binding sites, which results in the induction of different expression changes. However, the comparison allowed defining that despite these differences, the general properties of OSKM binding in both species are shared, like their binding to distant regions from promoters. Most importantly, in both species these similar mechanisms in molecular properties give result to the same output of activating the regulatory network of the pluripotency leading to the reprogramming to similar cell types, suggesting that the pluripotency network regulation and mechanisms to reactivate it has diverged significantly between the two species. [155]

Overall, despite the identification and study of the OSKM factors has helped to provide important knowledge and insights about the mechanisms involved in inducing pluripotency, much remains to be learned from the exact roles of each OSKM factor during reprogramming and the differences between both species. Thus, further investigations to dissect their particular properties and functions is needed to elucidate the mechanisms through which these set of transcription factors lead the reprogramming process of somatic cells towards pluripotency.

1.6 OCT4: a versatile transcription factor

Since its first discovery as a master regulator of pluripotency [161, 162], the transcription factor OCT4 has been extensively studied, being described to be crucial during mouse embryogenesis, in the establishment and maintenance of pluripotency *in vivo* and *in vitro*, and being part of the group of transcription factors that can lead to the generation of induced pluripotent stem cells.

1.6.1 OCT4 Structure

OCT4 belongs to the class V of the POU family of transcription factors, which are DNA binding proteins that are able to recognize the consensus octamer motif sequence 5'-ATGCAAAT-3'[163]. As a modular protein with functionally independent domains, OCT4 comprises three main domains: a central POU domain flanked by an N-terminal and a C-terminal transactivation domain (TADs). The POU domain contains a POU specific (POU-S) and POU homeodomain (POU-HD) separated by a linker containing a rigid helix and a flexible region and together comprise a bipartite DNA binding domain (DBD) [163] (Fig 1.6a). Structurally, the POU-S domain consist of four α-helices and binds the DNA sequence 5'-ATGC-3'; while the POU-HD domain consists of three α-helices and binds the DNA sequence 5'-AAAT-3' [164] (Fig. 1.6b), while the transactivation domains display high proline and glycine residues in the N-terminus and proline, glycine and serine/threonine-rich region in the C-terminus and are responsible for the interactions of OCT4 with other proteins [162].

OCT4 is encoded by the gene *POU5F1* in human, and *Pou5f1* in mouse. In human, *POU5F1* presents alternative splicing generating three isoforms OCT4A, OCT4B and OCT4B1. OCT4A (OCT4 in this thesis) is localized in the nucleus and is the only isoform involved in pluripotency maintenance and the only one involved in the induction of pluripotency to iPS [165, 166]. Besides alternative splicing, post-translational modifications are responsible for regulating the stability, function and localization of OCT4, such as phosphorylation, O-glycosylation and ubiquitination (Fig. 1.6a) [167-170].

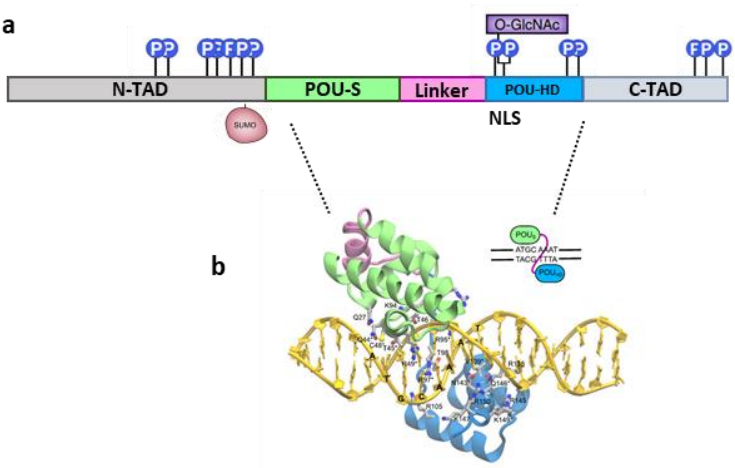


Fig. 1.6 OCT4 protein domains. a. Diagram representing the different domains of OCT4. OCT4 has a bipartite POU DNA-binding domain comprising a POU-specific DNA-binding domain (POU-S) and a POU-homeodomain (POU-HD) separated by a linker containing a rigid helix and a flexible region. The central POU domain is flanked by two transactivation domains located N-terminal (N-TAD) or C-terminal (C-TAD). Predicted post-translational modifications are shown. b. Model of POU/DNA complex. POU-S is shown in green, POU-HD in blue, linker in pink. This diagram was adapted from [163]. NTD = N-terminal transactivation domain, CTD = C-terminal transactivation domain, POU = POU domain, NLS = Nuclear Localization Signal.

1.6.2 OCT4 in the reprogramming process: Overcoming epigenetic barriers

Additionally to its fundamental function in the maintenance of pluripotency (discussed in section 1.4), OCT4 is also a central component needed for the reprogramming of somatic cells towards pluripotency and although its exact mechanisms are still not fully understood, it has been associated to multiple processes needed for the reprogramming. For instance, as discussed before, in human early stages of the reprogramming, OCT4 functions as a pioneer transcription factor, facilitating the opening of repressed chromatin relying on its capacity to target part of its canonical motif on nucleosome-enriched sequences in the somatic chromatin [110, 157]. However, it is still not well established what additional mechanisms are required to transition these initial engagement events into functional regulatory elements and thus establish new transcriptional networks needed to drive the reprogramming process. The formation of context-dependent complexes along with OCT4 could be one of the ways this transition is happening, involving the recruitment of epigenetic modulators, chromatin modifiers, and proteins involved in recruiting the RNA polymerase [171]. For instance, the capacity of OCT4 of not only recognize and bind DNA in different chromatin states, but its capacity

to recruit other transcription factors and interact with other proteins to establish complexes to drive the transcriptional regulation have been reported in mESC. By using mass spectrometry based studies different approaches have been conducted to identify the protein partners of OCT4 in mESC, expanding the regulatory network involved in pluripotency maintenance [82, 172, 173].

1.6.3 OCT4-centered protein interaction networks in mouse embryonic stem cells

The identification of interacting partners of OCT4 in mESC has been approached by different protocols and different systems, providing important information about the components of the pluripotency network but with the disadvantage of being little overlap between the proteins identified and with the necessity of replacing OCT4 with a tagged version for its purification (Table 1.1) [163]. The first approaches for defining the OCT4 interactomes depended on epitope-tagging affinity purification yielding different number of interactors. In order of publication, van der Berg *et al.* identified 54 [82], Pardo *et al.* 92, [172] Ding *et al.* 198 [174], and Esch *et al.* more than 600 OCT4 interaction partners [21]. When compared only 10 proteins were shared in all four studies (Chd4, Ctbp2, Hcfc1, Hdac1, Hells, Mta2, Mta3, Ogt, Smarca4, and Smarcc1). These discrepancies are most likely due to the different protocols employed (Table 1.1). van der Berg *et al.* and Ding *et al.* based their interactomes using cell lines derive from ZHBTc4, which is a cell line that has both endogenous *Oct4* alleles disrupted, depending on a doxycycline-suppressible *Oct4* transgene [175]. In both studies, transgenic mESC lines were established, expressing either biotinylated OCT4 [174] or FLAG tagged OCT4 [82] to replace the doxycycline suppressible OCT4. Furthermore, both analysis performed nuclear extract purification with DNase to remove the remaining DNA and eliminate protein interactions mediated indirectly by DNA. Pardo *et al.* also established a mouse cell line with by integrating an OCT4 C-terminus tagged epitope consisting of a 3XF calmodulin binding peptide (CBP) separated by a two TEV cleavage sites (Oct4-FTAP) [172]. For this cell line, endogenous OCT4 was not modified meaning the tagged OCT4 was co-expressed with endogenous OCT4. Esch. *et al* approach, despite being the one with more hits, was the less described and characterized and it relied on nuclear extract after the ectopic overexpression of a strep-tagged OCT4 in OG2 mESC cell line, which harbours a GFP under control of the *Oct4* distal enhancer [84]. Moreover, besides the

methodologies differences, the protein levels of OCT4 were variable among the protocols, which could contribute to the differences, as to maintain pluripotency the levels of OCT4 must be tightly controlled [176]. For instance, in Pardo *et al.* and Esch *et al.* the endogenous OCT4 was not modified, meaning cells were expressing both the endogenous and tagged OCT4. In Pardo *et al.* the levels of OCT4 were 30% or those of endogenous OCT4, but this seemed not to interfere with the ESC phenotype, as morphology and expression of ESC markers were similar to the original cell line with no transgene [172]. In contrast, in Ding *et al.* the levels of biotinylated OCT4 were less than the dox-regulated OCT4 but they report that it was still within the range to functionally maintain the mESC [174]. On the other hand, in van der Berg *et al.*, quantification was not provided but they also report no effects in the maintenance of mESC [82]. Lastly, for Esch *et al.* no quantification or characterization of the cells was provided (Resume in Table 1.1) [84]. Altogether, these variables, along with the biases and specificities of the mass spectrometry instruments, could be the main reason of the extremely low overlap of OCT4 interactors. For instance, one of the biggest discrepancies found was the absence of the remaining components of the core pluripotency network NANOG and SOX2, even when their interactions have been previously described at the proteomic and genomic co-binging level [152, 177, 178]. NANOG was not present in any study and SOX2 only in one. This lack of identification may be a result of mass spectrometry technical particularities, as for NANOG is has been proposed to be relative resistant to trypsin digestion, whereas for SOX2 it could be the result of weak interactions that require DNA to be stabilized [174].

The latest OCT4 pluripotency interactome overcame most of the general limitations of the previous approaches, while achieving a specific chromatin-associated proteins purification for the core transcriptional factors OSN. In this study, Rafiee *et al.* established a new protocol called Chromatin Immunoprecipitation for the Selective Isolation of Chromatin Associated Proteins (ChIP-SICAP), which does not require epitope tagging and the use an exogenous expression system, as it relied in the endogenous expression of OSN in mESCs for the immunoprecipitation (Table 1.1). Importantly, this protocol aimed to identify the proteins that associate with OSN in the context of chromatin which is more relevant to transcription regulation. Taking advantage of traditional ChIP protocols,

which rely on crosslinking to maintain protein-DNA interactions and promote the solubilisation of chromatin by sonication, ChIP-SICAP allowed the identification of chromatin-bound proteins close to OSN on short stretches of DNA (~200-500bp) while allowing the in parallel purification of DNA for next-generation sequencing, a step not allowed by other ChIP coupled with MS protocols [153, 179-182]. Specifically, 525 proteins were identified to interact with Oct4 on chromatin, including 8 out of the 10 that overlapped in the previous OCT4 mESC and adding 312 proteins not identified in any of the other studies.

Table 1.1 Summary of the published OCT4 interactomes studies in mESCs.

Study	Purification method	Cell source	Identified proteins	Fraction used	Trans-gene	Tag	OCT4 levels
Van der Berg *et al.* (2010) [82]	Affinity tag purification	ZHBTc4	54	Nuclear	Yes	Flag	N/A
Pardo *et al.* (2010) [172]	Affinity tag purification	mESCs (AB2.2)	92	Whole cell	Yes	Flag	Endogenous and transgene
Ding *et al.* (2012) [173]	Affinity tag purification	ZHBTc4	198	Nuclear	Yes	Biotin	Only transgene (Less than endogenous)
Esch *et al.* (2013) [84]	Affinity tag purification	OG2	> 600	Nuclear	Yes	Strep tag	N/A
Rafiee *et al.* (2016) [179]	ChIP-SICAP	mESCs (46c)	525	Chromatin	No	Used endogenous OCT4	Endogenous

Despite the differences between all mESC interactomes, a degree of consistency has been observed in the cellular processes of these identified proteins. First, the interactors shared between all interactomes included members of the SWI/SNF: Smarca4 and Smarcc1 and members of the NuRD family: Chd4, Mta2 and Mta3 increasing the overall confidence in the biological significance of these proteins. Moreover, the classification of the different proteins included five main groups: transcription factors important for pluripotency maintenance, chromatin remodelers, and proteins involved in signalling pathways, transcriptional co-activators part of the basal transcriptional machinery and proteins involved in DNA repair, recombination and repair [82, 172].

Interesting associations between OCT4 and members of the pluripotency network were further expanded in van den Berg *et al.,* linking OCT4 to more pathways. In this study, further identification of interactions of ESRRB, which was identified as an OCT4 binding partner, revealed proteins member of the Mediator complex, including RNA polymerase II subunits, and other transcription factors, such as TATA-box binding protein and TFIID. Therefore, ESRRB interaction with OCT4 could be linking the formation of the transcriptional machinery in genes regulated by OSN [82]. In fact, the Mediator complex has been identified along the masters regulators OSN, ESRRB and KLF4 in large enchanter domains known as super enhancers of pluripotency genes [153]. The mediator has also been shown to induce phase separated proteins condensates containing OSN to activate gene expression [183]. Furthermore, RNA polymerase II was identified in OCT4 ChIP-SICAP [179].

Noteworthy, despite discrepancies, all the studies correlated in the identification of chromatin remodelling complexes and histone modifiers, linking their importance for the pluripotency maintenance to the core pluripotency network, especially the esBAF (a stem cell specific SWI/SNF complex), NuRD, Polycomb, LSD1 and WDR5 (part of the MLL complex) [82, 84, 172, 173]. What is more interesting is that this complexes have been associated with the reprogramming process, and their interaction with OCT4 could help explain at some level how OCT4 is promoting the changes in the chromatin landscape and transcriptional network during the reprogramming process.

1.6.4 Integrative model of the involvement of OCT4 in pluripotency genes activation in reprogramming

A model integrating the evidence of the effects of the chromatin remodelers in the reprogramming process, the interactions described previously in the OCT4-interactome studies and the pioneer activity of OSK could be drawn to try to explain the transcriptional activation of silent pluripotency genes in the reprogramming process (reviewed in [171])(Fig. 1.7). This model includes the activation of a CpG island containing promoters of pluripotency associated genes that are activated by a distal regulatory element (enhancer) containing the DNA motifs for OSK. In somatic cells, the CpG island is repressed and contains the repressive mark H3K27me3, whereas the enhancer could

be high or low methylated but condensed in nucleosomes with no obvious histone modifications that could be associated with repressors. When OSK are induced, initial engagement by the recognition of the partial motifs in the nucleosomes lead to local nucleosome breathing allowing the binding of other TFs. After the recruitment of epigenetic modifiers, this results in gradual epigenetic remodelling by initially acquiring H3K4me1 and H3K4me2 and subsequently promoting the methylation of H3K4 at the promoter region, mediated by WDR5 (MLL complex) in parallel with the removal of the repressive mark H3K27me3 by UTX. At this time point, the transcription of the target gene is still not active, which may be due to the continuous repressive forces by the NuRD complex, which inhibits the nucleosome eviction. Moreover, for the gene activation, the need of yet unknown factors that cooperate with OSK help the eviction of nucleosomes resulting in the canonical signature of enhancers, meaning the presence of H3K4me2 and H3K27ac, being stabilized by the esBAF complex BRG1 (which has already being associated to help the pioneer activity of OCT4 in mESC [184]). Then, the recruitment of the co-activators Mediator and cohesion complexes establish the topological linkage of the enhancer and the promoter, and supressing the effects of the NuRD complex, although it remains associated with the enhancers. Finally, the recruitment of the transcription machinery and additional unknown factors activate and induce the expression of the target gene (Fig. 1.4) [171].

While this model integrates a growing body of evidence generated by characterizing OCT4 in pluripotency maintenance and reprogramming, there are still some limitations and important unanswered questions. First, the low overlap between the OCT4 interactome studies needs to be addressed before the function these proteins can be associated with OCT4 function in pluripotency. Second, protein interactome of OCT4 during reprogramming must be defined, as it might be very different from that in ES cells, similar to the report of differences observed in the initial engagement of OCT4 with the somatic genome compared to the ES genome [110, 154]. This is necessary to unravel new reprogramming-specific factors that are being recruited as a mechanism to help the OSKM factors to reshape the chromatin landscape to acquire the final pluripotent state (Fig 1.4, Fig. 1.6, and Fig. 1.7). Additionally, the identification of new reprogramming-

specific partners could lead to uncover new functions and biological processes none previously described for OCT4.

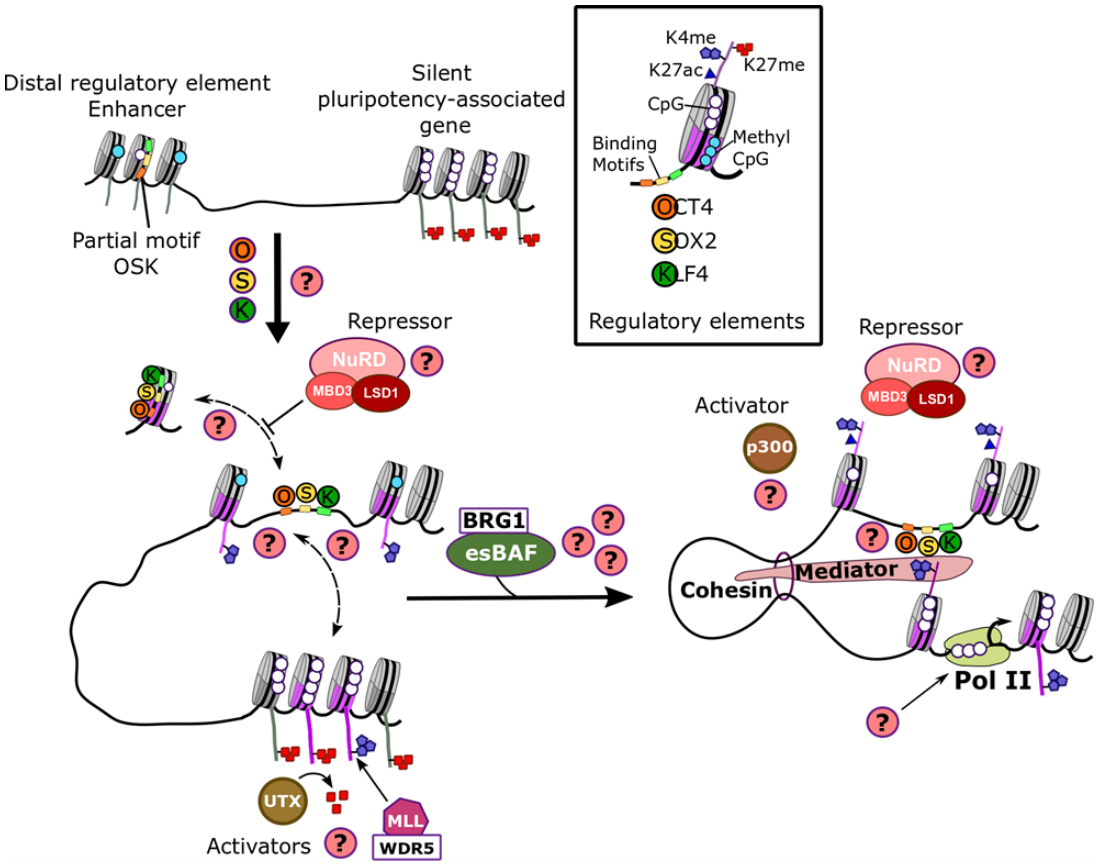


Fig. 1.7 OCT4, SOX2 and KLF4 (OSK) transcriptional activation of silent pluripotency genes at early reprogramming. Diagram representing the steps required to activate pluripotency-associated genes that are epigenetically modified with the repressive mark H3K27me3. First, pioneer factors OSK cooperatively bind to partial motif sequences enclosed in distal regulatory elements in closed chromatin, driving epigenetic remodelling by the deposition of H3K4me1 and H3K4me2. Initial OSK engagement also promotes the deposition of H3K4 methylation at the promoters of pluripotency genes, mediated by WDR5. In parallel, the histone demethylase UTX removes the H3K27me3 mark. A roadblock of the reprogramming process involves the inhibition of nucleosome eviction and stable acetylation by the repressor NuRD (subunits MBD3 and LSD1). To achieve gene activation, esBAF subunit BRG1 and other unknown factors help stabilize OSK to evict nucleosomes and stablish the canonical enhancer signature with the marks H3K4me2 and H3K27ac (mediated by p300). Topological changes involving the Mediator and cohesion complexes link the promoter with the enhancer and directing the expression of the target gene, by the recruitment of RNA polymerase II (Poll II) and more unknown factors. Each step of gene reactivation involves multiple complexes and factors, most of which are still unknown and are represented by the question marks in pink circles. Image modified from [171].

Third, and most importantly, since stem cell and cellular reprogramming research started, the main goals of their applications have being motivated by their potential for regenerative medicine approaches, such as drug screening, disease modelling and the promise of personalised cell therapies. Nevertheless, there is still a gap in our knowledge of human pluripotency, which is lagging behind the mouse model where most of the proteomic approaches have focused so far.

1.7 Aims of this thesis

- Define OCT4 protein interactors at early stages of reprogramming to iPSCs and during pluripotency maintenance.
- Define the role of essential and non-essential regions of OCT4 transactivation domains for its proteomic and genomic engagement at early stages of reprogramming.
- Compare the OCT4 pluripotency maintenance network against the early reprogramming one and identify key molecular interactions that are most relevant in the reprogramming process.

Chapter 2 MATERIAL AND METHODS

2.1 Reagents

Cell culture

Glasgow Minimum Essential Media (GMEM) (Sigma Aldrich #G5154)
Foetal Calf Serum (FCS) (Gibco #10270-106)
Sodium Pyruvate (Gibco #11360-039)
Glutamine (Gibco #25030-024)
Non e aa (Invitrogen 11140-036)
2-mercaptoethanol (50 mM Life technologies #31350010)
Pen strep (Invitrogen #15140-122)
Laminin 521 (BioLamina #800110)
SILAC Protein Quantitation Kit (LysC) – DMEM:F12 (Thermo Fisher # A33970)
KnockOut™ serum Replacement (Gibco # 10828028)
bFGF (Peprotech 100-18B)
DPBS, calcium, magnesium (Gibco™ # 14040133)

Lentivirus production

Fugene6 (Omega #E2691)
Opti-MEM™ Reduced Serum Medium (Gibco™, #31985062)
Lenti-X Concentrator (Takara #631232)
Polybrene (Sigma, #H9268-5G)

Rescue and Reprogramming

Alkaline phosphatase staining (Sigma # SCR004)
VitC (Sigma Aldrich, #A92902)

Western Blot

RIPA lysis buffer (Thermo Scientific™ #89901)
Pierce™ BCA Protein Assay Kit (Thermo Scientific™ #23225)
NuPAGE™ LDS Sample Buffer (4X) (Invitrogen™, #NP0007)
Bolt 10X Reducing agent (Invitrogen™, 10X Bolt™ Sample Reducing Agent #B0009)
Bolt™ 4-12% Bis-Tris Plus Gel (Invitrogen™, 10-well #NW04120BOX)
1X Bolt™ MES SDS Running Buffer (Invitrogen™, #B0002)
Immobilon-P PVDF Membrane (Millipore, IPVH00010)
Mini Blot Module (Invitrogen™, B1000)
1X of NuPAGE™ Transfer Buffer (Invitrogen™, #NP00061)
Bolt™ Antioxidant (Invitrogen™, BT0005)
Skim milk powder (Fisher #10651135)
PBS Tablets (Fisher #12821680)
TWEEN® 20 (Sigma #P7949-500ML)
SuperSignal™ West Pico chemiluminescent substrate (Thermo Scientific™ #34578)
Amersham Hyperfilm ECL 18 × 24 cm. GE # 28906836

Immunocytochemistry
Donkey serum (Sigma-Aldrich, #D9663)
Goat serum (Sigma-Aldrich, #G9023)
DAPI (Invitrogen™, #D1306)
Fluoromount-G™ (Invitrogen™, #00-4958-02)

ChIP-SICAP and ChIP-seq
DSG (Thermo #20593)
cOmplete Ultra Protease Inhibitor (Roche #05892791001)
Formaldehyde (Pierce, #28906)
Protein G Dynabeads™ (Invitrogen™ #10004D)
Terminal Deoxynucleotidyl Transferase (Thermo Scientific™ #EP0161)
Biotin- 11-ddUTP (1mM stock, Jenabioscience, NU-1619-BIOX-S)
Streptavidin beads (NEB, S1420S)
Vivacon 500 spin column (30K cartridge Sartorius, VN01H22)
RapiGest SF (Waters #186001861)
Lys-C (Wako, #125-05061)
Trypsin (Promega, #V5280)
Sera-mag beads (65152105050250 and 45152105050250)

Immunoprecipitation
Anti-FLAG® M2 Magnetic Beads (Millipore #M8823-5ML)
Benzonase® Nuclease (Millipore, #E1014-25KU)
SYPRO™ Ruby Protein Gel Stain (Invitrogen™, #S12000)
GelCode™ Blue Safe Protein Stain (ThermoFisher #24594)

Mass spectrometry
NuPAGE Novex 4-12% Bis-Tris gel (Life Technologies, #NP0321BOX)
Instant™ Blue Coomassie (Expedeon, SKU: ISB1L)
Lyophilised Trypsin Protease (Pierce™ Trypsin Protease, MS Grade #90057)
Empore Disk C18 Octadecyl (C18)-bonded silica (C18, #2215, 3M)
Iodoacetamide (Sigma, I1149-5g)
Ammonium Bicarbonate (NH4HCO3-Sigma, A6141-500G-D)

ChIP DNA purification
RNase A Solution (Millipore #70856)
Proteinase K Solution (Invitrogen™, #AM2548)
Phenol:Chloroform:Isoamyl Alcohol (Sigma-Aldrich, #P2069)

Library preparation
Qubit 2.0 HS dsDNA quantification kit (ThermoFisher, #Q32854)
NEBNext Ultra II Library Preparation Kit (NEB #E7645S)
NEBNext Ultra II Library Preparation Kit with Dual Index Primers (NEB #E7600S)

SpeedBeads™ magnetic carboxylate modified particles (Sigma-Aldrich, #GE65152105050250)
Agilent 2200 Tapestation with D1000 HS reagents (Agilent #5067-5584, #5067-5585)

Cloning
T4 DNA Ligase (NEB, #M0202S)
BsmBI (NEB, #R0580S)
SfiI (NEB, #R0123S)
BamHI (NEB, #R3136S)
XbaI (NEB, #R0145S)
In-Fusion® HD Cloning Kit (Takara, #638909)
EcoRI (NEB, #R3101S)
BbsI (NEB, #R0539)
NotI (NEB, #R3189S)
Shrimp Alkaline Phosphatase (rSAP) (NEB, #M0371S).

2.2 Methods

2.2.1 Cell Culture

Human Fibroblasts 176 (HF 176)

HF 176 were obtained from RBiomedical and cultured in GMEM supplemented with 10% FCS, 1X 13 non-essential amino acids, 1 mM Sodium Pyruvate, 1 mM glutamine and 0.1 mM 2-mercaptoethanol at 37°C and 5% CO_2. Medium was changed every 2-3 days and cells were passaged every 4-5 days using Trypsin+EDTA.

Human Fibroblasts SILAC

HF 176 were cultured in "Heavy" DMEM:F12 for SILAC supplemented with 10% dialyzed Foetal Bovine Serum (FBS) for SILAC, 1 mM Sodium Pyruvate, 1 mM glutamine, 1X Non-Essential Amino Acids, 0.1 mM 2-mercaptoethanol, 0.46 mM $^{13}C_6$ L-Lysine-2HCl (heavy) and 0.47mM L-Arginine-HCl (light) at 37°C and 5% CO_2. Before addition, medium was filtered using a 0.22µm filter. Medium was changed every 2-3 days and cells were passaged every 4-5 days using Trypsin+EDTA.

Human Embryonic Stem Cells (hES)

Master Sheffield 7 (MS7) were obtained from Tilo Kunath's lab at passage 17 and were cultured in Essential 8™ Medium (Gibco #A2858501) in plates coated with Human Recombinant Laminin 521 (4µg/mL in DPBS with Ca^{2+} and Mg^{2+}) at 37°C and 5% CO_2.

Medium was changed every day and cells were passaged every 2-3 days using EDTA (0.5mM).

hES SILAC

MS7 were cultured in Laminin 521-coated plates in iMEF conditioned-SILAC "light" medium. SILAC "light" medium for hES was prepared using DMEM:F12 for SILAC supplemented with 20% KnockOut Serum, 1 mM glutamine, 1X Non-Essential Amino Acids, 100 µM 2-mercaptoethanol and 10 ng/mL bFGF. After preparation, hES "light" medium was conditioned in iMEFs changing and collecting the everyday for 7 days. Once all medium was conditioned, the isotopes were added: 0.46 mM L-Lysine-2HCl (light) and 0.47 mM L-Arginine-HCl (light). After, medium was filtered using a 0.22µm filter and used for MS7 growth at 37°C and 5% CO_2, supplemented again with 10 ng/mL bFGF before use. Medium was changed every day and cells were passaged every 2-3 days using EDTA (0.5mM).

Human embryonic kidney 293 cells (HEK 293)

HEK 293 were obtained from Keisuke Kaji lab and cultured in GMEM supplemented with 10% FCS, 1X non-essential amino acids, 1 mM Sodium Pyruvate and 1 mM glutamine at 37°C and 5% CO_2. Medium was changed every 2-3 days and cells were passaged every 4-5 days using Trypsin+EDTA.

Mouse embryonic stem cells ZHBTc4

mESC ZHBTc4 were obtained from Ian Chamber's lab and cultured in plates coated with 0.1% gelatine/PBS and GMEM supplemented with 10% FCS, 100U/mL LIF, 1 mM Sodium Pyruvate, 1 mM glutamine, 1X 13 Non-Essential Amino Acids, 0.1 mM 2-mercaptoethanol and 150µg/mL Hygromycin at 37°C and 5% CO_2. Medium was changed every 2 days and cells were passaged every 3-4 days using Trypsin+EDTA.

Mouse Embryonic Fibroblast (MEF)

WT MEFS

WT MEFS were derived by Elisa Hall-Ponselè (Soufi lab) and were grown in GMEM supplemented with 10% FCS, 1 mM Sodium Pyruvate, 1 mM glutamine, 1X non-Essential

Amino Acids, 0.05 mM, 2-mercaptoethanol, and Penn Strep (10000 U/mL pen, 10,000 µg/mL strep) at 37°C and 5% CO_2. Medium was changed every 2 days and cells were passaged once using Trypsin+EDTA.

iMEFs

Irradiated MEFs (iMEF) were thawed and kept overnight in plates coated with 0.1% gelatine/PBS in the WT MEF conditions described previously. Next day, SILAC hES media without the addition of the isotopes was added. Medium was changed every day as described in hES SILAC.

Cas9 TNG MKOS MEFs (Tg MEF)

Tg MEFS were obtained from Dan K (Keisuke Kaji's lab) and cultured as reported in plates coated with 0.1% gelatine/PBS and GMEM supplemented with 10% FCS, 1 mM Sodium Pyruvate, 1 mM glutamine, 1X non-Essential Amino Acids, 100 U/ml LIF (0.1 mM, 2-mercaptoethanol, Penn Strep (10000 U/mL pen, 10,000 µg/mL strep), 5 ng/mL FGF2 and 1µg/mL Heparin at 37°C and 5% CO_2. Medium was changed every 2 days and cells were passaged once using Trypsin+EDTA.

2.2.2 Lentivirus production and concentration

Virus Concentration

HEK293 were seeded at a density of 3 X 10^6 cells per 15 cm dish. Next day (~40% confluence) transfection was carried on using Fugene6 and a total of 15µg of DNA plasmids in a 3:2:1 ratio of the gene of interest vector (FU-tetO), psPAX2 packaging vector and pMDG envelope vector respectively. Mixed plasmids were dissolved in 90 µL Fugene6 and necessary Opti-MEM™ Reduced Serum Medium for a final volume of 1.8mL. Mixture was left to incubate for 15 minutes before adding it in a drop-wise fashion to the HEK293 cell culture. Sixteen hours post-transfection, the medium was replaced with 30mL of fresh HEK medium and cells were left in cultured. After 60hrs of the medium change, supernatant was collected, filtered through a 0.45 µM syringe filter (to remove cells and debris), mixed with the Lenti-X Concentrator at a ratio 3:1 and left incubating overnight at 4°C. Next day, the mixture was centrifuged at 1500 g for 2 hours.

Supernatant was discarded and pellet was dissolved in 200 µL of GMEM (plain medium with no supplements). To help dissolve the pellet, it was left with the GMEM overnight at 4°C. Next day mixture was then gently resuspended, aliquoted in small volumes (20-50µl) and stored at -80°C.

gRNA and TetO viral Supernatant Collection - Candidates

HEKs were seeded at a density of 7.5 X 10^5 cells per 10 cm dish. Next day (~40% confluence) transfection was carried on using Fugene6 as previously described for the virus concentration but using 5µg as the final plasmid DNA concentration, 30 µL Fugene 6 and necessary OPTI-MEM medium for a final volume of 600µl. 16 hours post-transfection, the medium was replaced with 10 mL of fresh medium and cells were cultured for 60 hr. Supernatant was collected and filtered through a 0.45 µM syringe filter, aliquoted in 1.5mL volumes and stored at -80°C.

Lentivirus titration

Concentrated Virus

To determine the virus titre from concentrated lentivirus, a concentrated lentivirus for constitutive GFP was used. HF176 were seeded at a density of 1x10^5 cells per well in a 6 well plate and cultured for 16 hrs. Concentrated constitutive GFP lentivirus was resuspended and diluted 10^{-2}, 10^{-3}, 10^{-4}, 10^{-6} and 10^{-6} into a final volume of 2mL of culture medium. Human fibroblasts were transduced with 2mL of each diluted supernatants. Polybrene was added to each infection at a final concentration of 4.5µg/ml. 16 hours post-infection medium was replaced and cells were cultured for 48 hours. %GFP cells and the virus titre was determined using FACS (BD LSRFortessa (4 laser)). Titre obtained from the constitutive GFP lentivirus was used as an estimate of the titre of the remaining lentiviruses.

Supernatant gRNA

To determine the virus titre from supernatant gRNA lentivirus, WT MEFs were seeded a density of 1x10^5 cells per well in a 6-well plate and cultured for 16hrs prior to transduction. For transduction, for each gRNA Lentivirus and aliquot was defrost and dilute 1/2, 1/4, 1/6 and 1/8 in MEF media with Polybrene at a final concentration of

4.5µg/ml. Cells were incubated with the virus for 8 hours before changing to MEF media and cultured for 48hrs. %BFP cells and the virus titre for each sgRNA was determined using FACS (BD LSRFortessa (4 laser))

2.2.3 Rescue assays ZHBTc4

ZHBTc4 cell lines were plated at a density of 10^7 in a 10 cm dish. After 6 hours cells were transfected 15 µg of the corresponding CAG plasmids (hOCT4 and 3XF OCT4). 12 hours post transfection cells were plated at a clonal density (10^6 cells per 10 cm dish). After 6 hours, knockout and selection was induced adding dox and puromycin (1µg/mL). Cells were cultured in the presence of dox and puromycin (1µg/mL) with daily medium change. Alkaline phosphatase staining was performed after 10 days. Colonies were count by hand and the rescue efficiency was determined from the ratio of alkaline positive mESC cell colonies in plus dox to those in minus dox. Three technical replicates were taken into account.

2.2.4 TNG MKOS (Cas9) MEF Reprogramming

Previously thawed and plated TNG MKOS Cas9 MEFs and WT MEF were mixed in a ratio of 10% TNG MEFs and 90% WT MEFs and plated at a density of $1x10^5$ cells per well in a 6 well plate pre-coated with 0.1% gelatine and incubated for 16h. Three replicates were plated per sgRNA and per TetO lentivirus. To transfect, sgRNA and Tet-O supernatant lentivirus for each candidate and controls were thawed before transfection and diluted to an appropriate titre to achieve ~85-90% transduction efficiency in mESC+fgf2 media with 4.5µg/mL polybrene. MEFs with lentivirus were incubated for 8 hours and media was changed to fresh mESC and incubated for 16 hours. Reprogramming medium was added 24 hours after, including ES media, 300ng/ml doxycycline, 10µg/ml VitC. Cells were incubated for 15 days with change every 2 days or every day when necessary at later stages. At day 15 wells were washed with PBS once, and 1mL PBS/well was added before imaging using the Celigo Imaging Cytometer (Nexelom Bioscience) using the green (GFP) and red (mOrange) filters. Images were post-processed using Fiji Is Just ImageJ (FIJI) [185]. GFP+ colonies were manually count, taking into account three replicates for each condition. Significance in changes in reprogramming efficiency were determined with a

paired student's t-test for each condition GFP+ colonies against the respective control (Zeo and No virus).

2.2.5 Protein purification

OSKM 48h for WB (3XFLAG WT, WT and mutants) - To test expression of OCT4 (3XFLAG WT, WT and mutants) and SOX2, KLF4 and cMYC by Western Blot, HF 176 were seeded at a density of $5x10^5$ cells in 10 cm dishes and transduced with concentrated OCT4 (WT or mutants) lentivirus, along with SOX2, cMYC, KLF4 and rtTA2M2 concentrated lentivirus at MOI of 5. 16 hours post-transduction, the medium was replaced and cells were cultured for 48 hours. OSKM protein expression was induced adding fresh medium with 1µg/mL of doxycycline into one dish of each factor infection. Cells were cultured for 48 hours before collection. For control samples, Human Fibroblasts without transduction of the virus were cultured and processed as the fibroblasts with virus. For total protein extraction 10 cm dishes were scraped and pelleted by centrifuging for 5-10 minutes at 500 × g. Media was removed and cells were washed twice with PBS. Cells were lysed on ice using 100-200ul RIPA lysis buffer containing cOmplete Ultra Protease Inhibitor and sonicated on high with Bioruptor in Cold room (6x10 sec intervals). Cell suspension was left for 15 minutes rotating in the cold room. Cells lysates were centrifuged for 15 minutes at max. speed (4°C) and transfer to protein LoBind tubes. Protein concentration was determined for each sample using the Pierce™ BCA Protein Assay Kit.

Chromatin-bound Proteins from Subcellular Fractions

To test candidates expression in chromatin by Western Blot, HF 176 were seeded at a density of $5x10^5$ cells in 10 cm dishes and transduced with concentrated OCT4 (WT or mutants) lentivirus, along with SOX2, cMYC, KLF4 and rtTA2M2 concentrated lentivirus at MOI of 5. 16 hours post-transduction, the medium was replaced and cells were cultured for 48 hours. OSKM protein expression was induced adding fresh medium with 1µg/mL of doxycycline into one dish of each factor infection. Cells were cultured for 48 hours before collection. For control samples, HF without transduction of the virus were cultured and processed as the fibroblasts with virus. For hES cells, 10 cm dishes were plated until 90% confluence. Cells were scraped and pelleted as described before for WB

Extraction was performed as reported [186]. Pellet was resuspended in 1mL of cold PBS and transferred to a 1.5 LoBind tube and centrifuged at 130 x g at 4 °C for 3 min. Cell pellet was lysed with 5 volumes of ice-cold E1 Buffer (50 mM HEPES-KOH pH 7.5, 140 mM NaCl, 1 mM EDTA, 10% glycerol, 0.5% NP-40, 0.25% Triton X-100, 1 mM DTT, 1X cOmplete Ultra Protease Inhibitor) for 1 volume of cell pellet. Cells were resuspended by gently pipetting up and down for 10 times before centrifugation at 1,100 *x g* at 4 °C for 2 min. Supernatant was collected in a new pre-chilled LoBind tube and labelled as the cytoplasm fraction. Pellet was resuspended in the same volume of buffer E1 used previously (5 volumes) and centrifuged immediately at 1,100 *x g* at 4 °C for 2 min. Supernatant was discarded and pellet resuspended by gently pipetting with same volume of buffer E1 (5 volumes). Tube was left for 10 min in ice before centrifugation at 1,100 *x g* at 4 °C for 2 min. Supernatant was discarded and pellet gently resuspended in 2 volumes of ice-cold E2 buffer (10 mM Tris-HCl pH 8.0, 200 mM NaCl, 1 mM EDTA pH 8.0, 0.5 mM EGTA, 1X cOmplete Ultra Protease Inhibitor protease inhibitor cocktail) for 1 volume of cell pellet, followed by centrifugation at 1,100 *x g* at 4 °C for 2 min. Supernatant was collected in a pre-chilled LoBind tube and labelled as the nucleus fraction. Pellet was resuspended in the same volume of E2 as before (2 volumes) and centrifuged immediately at 1,100 *x g* at 4 °C for 2 min. Supernatant was discarded, pellet was resuspended in the same volume of E2 as before (2 volumes) and centrifuged immediately at 1,100 *x g* at 4 °C for 2 min and left for 10 min on ice before centrifugation at 1,100 *x g* at 4 °C for 2 min. Supernatant was discarded and pellet was resuspended by pipetting in 2 volumes of ice-cold E3 buffer (500 mM Tris-HCl pH 6.8, 500 mM NaCl, 1 X cOmplete Ultra Protease Inhibitor protease inhibitor cocktail). Tubes were sonicated in the water bath sonicator in the cold Room for 5 min, 30 sec ON/30 sec OFF on maximum power. All fractions (cytoplasm, nuclear and chromatin) were centrifuged at 16,000 *x g* at 4 °C for 10 and supernatant was transferred to a new pre-chilled LoBind tube. Protein concentration was determined for each fraction using the Pierce BCA Protein Assay Kit.

2.2.6 Western Blot

For 3XFLAG OCT4 IPs (OCT4= WT and mutants) and HF control: To corroborate OCT4 elution in the IPs 5µl of each elution were loaded, 1 µL of input. (Triplicates for each sample)

Total extract OSKM 48h (OCT4= 3XFLAG WT, WT and mutants) and HF control: To test OSKM protein levels 5 µg of total protein were loaded.

Fractions OSKM 48h (WT and mutants), hES, and HF control: To test fractionations, 1 µg of Total Extract, cytoplasm extract, nuclear extract and chromatin extract were loaded. To analyse candidates, 5µg of chromatin fractions were loaded and 0.5 µg of the chromatin fraction were loaded to detect OCT4 and H3 as loading controls.

WB General Protocol

NuPAGE™ LDS Sample Buffer (4X) and Bolt Reducing agent (10X) were added to each sample for a final concentration of 1X. Samples were heated at 70°C for 10 minutes. Required volume was loaded into a Bolt™ 4-12% Bis-Tris Plus Gel and ran at 200V for 30 min with 1X Bolt™ MES SDS Running Buffer. Proteins were transferred into a Immobilon-P PVDF Membrane at 30V for 90 min using the Mini Blot Module in 1X of NuPAGE™ Transfer Buffer, 20% MetOH and Bolt™ Antioxidant. Membrane was blocked overnight at 4°C with 10% Skim milk powder in PBST (PBS 1x + TWEEN® 20 0.1%). Primary antibody incubations (in 5% BSA) were left overnight followed by 5X min washes with PBST. Secondary antibody incubations with HRP conjugates in PBST were performed for 1hr at room temperature. After 5X 5min washes with PBST, WB were visualized by using SuperSignal™ West Pico chemiluminescent substrate and X-ray film developer (Film= Amersham Hyperfilm). All antibodies used and dilutions are listed in Table 2.1 and 2.2.

2.2.7 Immunocytochemistry (IC)

HF176 were seeded at a density of $2.5x10^4$ cells per well in a 12 well plate, cultured for 16 hrs and transduced with O (WT or 3XFLAG), S, K, M and rtTA2 lentiviruses at a MOI of 5. Polybrene was added to each transfection at a final concentration of 4.5µg/ml. 16 hours post-transduction, the medium was replaced, cells were cultured for 48 hours. OSKM expression was induced adding fresh medium with 1µg/mL of doxycycline. Cells were cultured for 48 hours and analysed using Immunocytochemistry. Cells were fixed in

4% paraformaldehyde for 10 min at room temperature, permeabilized with 0.1% Triton X-100 for 10 min at room temperature and blocked for nonspecific binding with 44% Donkey or Goat serum in PBS for 60 min at room temperature. Overnight incubations at 4^{o}C were performed with anti-hOCT4 antibody, hSOX2 antibody, hKLF4 antibody, c-MYC antibody. Primary antibodies were diluted in 4% Donkey or Goat serum in PBS. Cells were washed 3X with TBST (TBS=50 mM Tris-Cl pH 7.5, 150 mM NaCl + 0.05% Tween 20). Cells were incubated with secondary antibodies anti-goat Alexa Fluor 488 donkey, anti-rabbit Alexa Fluor 488 goat, for 1 hour at room temperature and washed 3X with TBST. Nuclei were counterstained with 3 μg/ml of DAPI for 10 min at room temperature. Cells were washed 1X with MiliQ. Fluorescence images were taken using the iRiS™ Digital Cell Imaging System (Logos Biosystems, Inc.), using DAPI and a GFP filter for green fluorescence. All antibodies used and dilutions are listed in Table 2.1.

2.2.8 Immunocytochemistry for confocal

Centre Optical Instrumentation Laboratory (COIL) facilities (Wellcome Trust Centre for Cell Biology – Kings Buildings – The University of Edinburgh) with the help of Dr David Kelly.

HF176 were seeded at a density of 2.5x10^{4} cells per well in a glass coverslip inside a 12-well plate. Cells were cultured for 16 hrs before transduction with O (WT or mutants), S, K, M and rtTA2 lentiviruses at a MOI of 5. Polybrene was added to each transfection at a final concentration of 4.5μg/ml. 16 hours post-transduction, the medium was replaced, cells were cultured for 48 hours. OSKM expression was induced adding fresh medium with 1μg/mL of doxycycline. Cells were cultured for 48 hours before fixed in 4% paraformaldehyde for 10 min at room temperature, permeabilized with 0.1% Triton X-100 for 10 min at room temperature and blocked for nonspecific binding with 4% Donkey or Goat serum in PBS for 60 min at room temperature. Overnight incubations at 4^{o}C were performed with anti-hOCT4 antibody (2.5 μg/ml). Cells were washed 3X with TBST (TBS=50 mM Tris-Cl pH 7.5, 150 mM NaCl + 0.05% Tween 20) and incubated secondary anti-rabbit Alexa Fluor 488 goat (1:50000) for 1 hour at room temperature. Cells were washed 3X with TBST and once with water before mounting. Coverslips were mounted onto glass slides with Fluoromount-G™. Images were acquired with Zeiss LSM 880 with

Fast Airyscan microscope with a 100x objective using Zen Black acquisition software with GFP filter. Images were post-processed using Fiji Is Just ImageJ (FIJI) [185]. All antibodies used and dilutions are listed in Tables 2.1 and 2.2.

Table 2.1 Primary Antibodies used for the Western Blot, Immunocytochemistry (IC), ChIP-SICAP and ChIP-seq experiments.

Primary Antibodies	Company and Catalogue Number	Host Species and type	Dilution
GAPDH HRP-conjugate	CST #8884	Rabbit monoclonal	1:5000 (WB)
TNIP2	ProteinTech #15459-1-AP	Rabbit polyclonal	1:1000 (WB)
XPO6	Abcam #ab72333	Rabbit polyclonal	1µg/ml (WB)
ETV4	Thermo (Invitrogen™) # PA5-79223	Rabbit polyclonal	0.5 µg/mL (WB)
KDM4B	LSBio #LS-B13472	Rabbit polyclonal	1:1000 (WB)
UFD1L	ProteinTech #10615-1-AP	Rabbit polyclonal	1:1000 (WB)
Histone H3	Abcam #ab24834	Mouse monoclonal	1:10000-1:20000 (WB)
OCT4	Abcam #ab19857	Rabbit polyclonal	1 µg/mL (WB) 2.5 mg/ml (IC) 2.5 µg/ml (IC confocal)
SOX2	R&D #AF2018	Goat polyclonal	0.4µg/mL (WB) 5 mg/ml (IC)
cMYC	R&D systems #AF3696	Goat polyclonal	1:300 (WB) 10 mg/ml (IC)
KLF4	R&D systems #AF3640	Goat polyclonal	0.2 µg/mL (WB) 2.5 mg/ml (IC)
IgG Isotype Control	Abcam #ab37415	Rabbit Polyclonal	Used for ChIP-SICAP control
Lamin (Donated by Julia W, Lowell lab)	Abcam #ab16048	Rabbit Polyclonal	0.5 µg/mL (WB)

Table 2.2 Secondary Antibodies used for the Western Blot, Immunocytochemistry, ChIP-SICAP and ChIP-seq experiments.

Secondary Antibodies	Company and Catalogue Number	Dilution
Goat Anti-Mouse IgG-HRP	SantaCruz #sc-2005	1:5000 (WB)
Goat Anti-Rabbit IgG-HRP	SantaCruz #sc-2004	1:5000 (WB)
Donkey Anti-Goat IgG-HRP	Santa Cruz #sc-2020	1:5000 (WB)
Goat Alexa Fluor 488 Anti-Rabbit IgG	Abcam #ab150077 Ex: 495nm, Em: 519	1:500 (IC) 1:10000 (IC confocal)
Donkey Alexa Fluor 488 anti Goat IgG	Abcam #ab150129 Ex: 495nm, Em: 519	1:500 (IC)

2.2.9 Proteomics

ChIP-SICAP (Reported protocol) [179] (See Figure 3.1 for diagram)

Cross-link, cell lysis and sonication- 25 million human embryonic stem cells (MS7) and 25 million HmFb (HF) were pelleted and re-suspended in 1.5% fresh Formaldehyde (Pierce) in PBS. After 15 min incubation at room temperature with occasional rotations, 125mM Glycine was added to the solution to quench cross-linking. Then the cells were washed twice with PBS and resuspended in 900 µl TE buffer (10mM Tris-HCl pH 8, 1mM EDTA pH 8) plus cOmplete Ultra Protease Inhibitor and kept on ice for 5min. Then 100 µl Triton X-100 10% was added and cells were incubated another 5min on ice. Cells were washed twice by resuspending them in 10mM Tris-HCl (pH = 7.5), spinning afterward at 500g for 5min, and removing the supernatant). Samples were resuspended in 10mM Tris-HCl to a final volume of 1mL and sonicated using a Covaris M220 sonicator. Sonication was done in 10 min intervals and 50µl of sonicated chromatin were collected after each 10 min cycle to test sonication quality in an agarose gel electrophoresis. hES were sonicated up to 2 hrs and HF up to 3 hrs. After the final sonication cycle, samples were centrifuged at 12000g for 10min to sediment cell debris, and collection of the supernatant.

OCT4 ChIP and biotinylation- Shredded chromatin was incubated with 30µL of Protein G Dynabeads™ saturated with 10 µg of OCT4 antibody and left rotating in the cold room for overnight. After beads were washed once with 10mM Tris-HCl, and once with 1xTdT buffer. Beads were resuspended in 1xTdT buffer, 60 U of Terminal Deoxynucleotidyl Transferase and 50µM of Biotin- 11-ddUTP, and incubated at 37°C for 30min. Subsequently the beads were washed 6 times with ice-cold IP buffer, resuspended in 200mM of DTT and 7.5% of SDS, and incubated at 37°C for 30min. Then the beads were removed and the supernatant was collected adjusting the volume to 1.5 mL with IP buffer. 50 µl of Streptavidin beads were added, and the samples were rotated 30min at room temperature. After rotation head-to-tail, the beads were washed 3 times with 1% SDS, once with 2M NaCl, twice with 20% isopropanol, and 5 times with 50% acetonitrile.

Reverse Cross-link and protein digestion - The beads were resuspended in 0.1% RapiGest and 5mM DTT. To reverse the cross-links, the beads were boiled at 95°C for 20min followed by adding 10mM iodoacetamide to the solution. After 30min incubation 5mM

DTT was added to the solution. Then 250ng Lys-C and 1µg Trypsin were added to the samples to digest the proteins overnight at 37^{o}C

Peptide and DNA purification - Supernatant with peptides was collected from the beads and cleaned by SP3 protocol to separate the peptides for MS and the DNA for qPCR analysis. SP3 beads were prepared by mixing 2x20µl of Sera-Mag beads in a 0.2-ml PCR tube. Beads were washed three times with 160µl of dH2O. Beads were resuspended in 100µl of dH2O (note: the beads could be stored for 2 weeks in the fridge). 2µl of the SP3 beads were added to the peptides and vortex. Then 200 µL of acetonitrile (ACN) 100% were added. Samples were vortexed and spin briefly. 20µl of ACN 100% were added and beads were left for 10 min before putting in the magnet. Liquid was collected for DNA isolation and 200 µL of ACN 100% were added to the beads. Liquid was discarded from the beads followed by a brief spin of the beads to discard all the residues of ACN. Once all the ACN was removed, 10µl of DMSO 2% were added on the walls of the tubes without pipetting. Beads were vortex vigorously and spin for a few seconds. Beads were removed and supernatant was transferred to tubes with 1µl of formic acid 1% and stored at -80^{o}C until MS analysis. To recover DNA after digesting the proteins the liquid collected in the SP3 clean-up protocol containing the DNA was drown out using a speed vac. DNA was then reconstituted using TE buffer. DNA was cleaned using Sera-mag beads and resuspended in a final volume of 20µL of Tris-Cl 10mM without EDTA for qPCR analysis. DNA was quantified by Qubit 2.0 using the HS dsDNA quantification kit.

ChIP SICAP (Modified protocol) (See Figure 3.3a for diagram)

Double Cross-link, cell lysis and sonication - Human Fibroblasts were seeded at a density of 1.5x10^{6} cells in 15 cm dishes and transduced with concentrated OCT4 (WT and mutants) lentivirus, along with SOX2, cMYC, KLF4 and rtTA2M2 concentrated lentivirus at MOI of 5. 16 hours post-transduction, the medium was replaced and cells were cultured for 48 hours. OSKM protein expression was induced adding fresh medium with 1µg/mL of doxycycline into one dish of each factor infection. Cells were cultured for 48 hours before Cross-link. For control samples, Human Fibroblasts without transduction of the virus were cultured and processed as the fibroblasts with virus. For hES, cells were grown in 15cm dishes until 90% confluence before Cross-link. Chromatin fragments were prepared from the 15 cm dishes (hES, OSKM 48h and HF). Before cross-linking DSG and

Formaldehyde were made fresh. To crosslink, cells were washed 3X with PBS at RT. After final wash, 15mL of PBS/$MgCl_2$ was added to each plate. 120µL of fresh DSG (0.25M stock prepared by adding 613µL DMSO to 50mg of DSG) were added to each plate to get a final concentration of 2mM. Plates were incubated at RT for 45min in a horizontal shaker with constant moving followed by 3X washes of PBS prior to the FA cross-link. After the last wash, 20 mL of PBS were added to each plate followed by adding 3mL of Formaldehyde crosslinking buffer (50mM HEPES-KOH, pH7.5, 100mM NaCl, 1mM EDTA, 0.5mM EGTA, 11% formaldehyde). Crosslinking was blocked by adding 1.65 mL 2.5M Glycine and incubating for 5 minutes at room temperature. Cells were harvested using a silicon scraper and centrifuged for 5 minutes at 1350 rcf at 4^{o}C. Cells pellets were then resuspended in 10mL Lysis Buffer 1 (50mM HEPES-KOH pH7.5, 140mM NaCl, 1mM EDTA, 10% Glycerol, 0.5% NP-40 Substitute, 0.25% Triton X100 and cOmplete Ultra Protease Inhibitor rotated for 10 minutes at 4^{o}C. Cells were disrupted using a tight 7mL dounce homogeniser with 80 strokes on ice. Nuclei were collected by centrifugation at 1350rcf for 5 minutes at 4^{o}C. The nuclei were washed in 10mL Lysis Buffer 2 (10mM Tris-HCl pH 8, 200mM NaCl, 1mM EDTA, 0.5mM EGTA and cOmplete Ultra Protease Inhibitor) for 10 minutes a rotator at room temperature. The nuclei were collected by centrifugation and resuspended in Lysis Buffer 3 (10mM Tris-HCl pH8, 100mM NaCl, 1mM EDTA, 0.5mM EGTA 0.1% Na-deoxycholate, 0.5% N-lauroylsarcosine and cOmplete Ultra Protease Inhibitor. Samples were sonicated using a Covaris M220 sonicator using a time of 90 min for hES and 140 min for HF and OSKM 48h. Sonication was done in 10 minutes intervals. To solubilise chromatin following sonication 100µL of 10% Triton X-100 was added per 1mL of sonicated chromatin. Before ChIP, 50µl of sonicated chromatin were collected to test sonication quality in an agarose gel electrophoresis.

OCT4 and IgG ChIP – For each ChIP, 70µL of Protein G Dynabeads were washed three times with PBS+0.02% Tween. The beads were saturated with 20µg of OCT4 antibody or IgG for hES Ctrl diluted in 600µL of with PBS+0.02% Tween by rotating for 6 hours at 4°C. The beads were then washed three more times in PBS+0.02% Tween. ChIP was carried out by incubating the beads with 120µg of chromatin overnight at 4°C (concentration of chromatin was estimated by purifying and quantifying DNA from the 50µL of sonicated chromatin used for visualization in the agarose gel). Beads were washed once with 10mM Tris-HCl, and once with 1xTdT buffer.

Biotinylation - The beads were resuspended in 1xTdT buffer, 4µL ddUTP-Biotin and 4µL of TdT enzyme and incubated at 37°C for 30min. Subsequently the beads were washed 6 times with ice-cold IP buffer (50mM Tris-HCl pH 8, 5mM EDTA, 1% Triton, 0.5% NP40, 150 mM NaCl), resuspended in 200mM of DTT and 7.5% of SDS, and incubated at 37°C for 30min. Then the beads were removed and the supernatant was collected. **NOTE: Two ChIPs were pooled at this stage for each replicate, meaning 240ug of initial chromatin from the same sample for each replicate.** Once two ChIPs were pooled, volume was adjusted to 1.5 mL with IP buffer and added to 50 µl of Streptavidin beads previously washed 3X with IP buffer. Samples were rotated 1h at room temperature. After rotation head-to-tail, the beads were washed 3 times with 1% SDS, once with 2M NaCl, twice with 20% isopropanol, and 4 times with 50% acetonitrile.

FASP - Beads were resuspended in 100µL of 0.1% RapiGest and 2.5µL of 1M DTT to get a final concentration of 25mM. To reverse the cross-links and digest the proteins, beads were boiled for 10 min at 95°C. Supernatant was collected in new Lo-Bind tubes and beads were discarded. 91.1 µg of Urea was added directly to the sample to a final concentration of 8M and shake until dissolved. FASP was done as described [187]. The solution was then transferred to a Vivacon 500 spin column and centrifuged for 15 min at 13,800g. Supernatant was discarded and 100µl of 0.05 M Iodoacetamide dissolved in 8 M urea (dissolved in 0.1M Tris-HCl pH 8.2) were added to the membrane and incubated at RT for 20 min protected from light followed by 10 min centrifugation at 13,800g. Membrane was washed with 100µl of 8M urea and centrifuged for 15 min at 13,800g. Next wash was performed with 100 µL of 0.05 M of ammonium bicarbonate (ABC) buffer in ultrapure water followed by a 15 min centrifugation at 13,800 g. Collection tubes were removed and the membrane column was placed in a new Lo-bind tube. To digest the proteins 1µg Trypsin (1µl – 1µg/µL) and 50ng LysC (2.5µl – 20µg/mL) in 100 µl 5 mM ABC buffer were added to the membrane column and incubated overnight at 37°C. To recover peptides, the membrane columns were centrifuged for 15 min at 13,800g. Supernatant was not discarded as it contained the digested peptides. Column was washed once with 100 µL of ABC buffer. Wash was not discarded and it was pooled with the digested peptides solution for storage at-20°C before MS.

Immunoprecipitation

Cell lysis - Human Fibroblasts were seeded at a density of $1.5x10^6$ cells in 15 cm dishes and transduced with concentrated 3XFLAG OCT4 (WT and mutants) lentivirus, along with SOX2, cMYC, KLF4 and rtTA2M2 concentrated lentivirus at MOI of 5. 16 hours post-transduction, the medium was replaced and cells were cultured for 48 hours. OSKM protein expression was induced adding fresh medium with 1µg/mL of doxycycline into one dish of each factor infection. Cells were cultured for 48 hours and pellet was collected. For control samples, Human Fibroblasts without transduction of the virus were cultured and processed as the fibroblasts with virus. Cells were scrapped in the cold room (4^oC), collected in 50 mL tubes and centrifuged at 1350 rfc for 10 minutes at 4^oC. Dishes were washed with cold PBS and scrapped again to recover most cells. Second wash was added to the pellet and centrifuged at 1350 rfc rpm for 10 minutes at 4^oC. If pellet is too pink wash with cold PBS once more. For protein extraction pre-cold all the buffers and PBS. Cells were resuspended in 1mL of IP lysis buffer (50 mM Tris-HCl pH 8, 100 mM KCl, 5 mM $MgCl_2$, 10 % glycerol, 0.5 % NP-40 (add fresh), 0.2 mM EDTA, 1X cOmplete Ultra Protease Inhibitor (add fresh)). Cells suspension was transferred into a 2 mL Dounce Homogenizer (cooled on ice) and 100 strokes with thigh pestle were applied, being careful with the bubbles. Cells were transferred into a cold 1.5 mL LoBind Tube and left in IP lysis buffer (with glycerol) for 30 min rotating in the cold room. Extract was centrifuged for 10 min centrifugation at max speed at 4°C, transfer supernatant containing the protein extract to a new cold LoBind tube. 50µl of the total extract were collected prior to the IP, to use for input analysis.

3XFLAG IP- For Immunoprecipitation all steps were carried on in the cold room. For each sample 170 µl of Anti-FLAG® M2 Magnetic Beads (previously vortexed for minimum one minute) were transferred to cold LoBind tubes. Anti-FLAG® M2 Magnetic Beads. Beads are more easily pipetted with a cut-off yellow tip, previously washed with MiliQ. Once collected, Anti-FLAG® M2 Magnetic Beads were washed 4X with 1mL of C-100* Buffer (HEPES (pH 7.6), 20 mM, Glycerol 10%, $MgCl_2$, 1.5 mM, KCl 100 mM, EDTA 0.2 mM, Protein Inhibitors 1X (add fresh), DTT 0.5 mM (add fresh), NP40 0.02% (add fresh)). For each sample, the 1mL extract was added to the washed beads. 6 µl of Benzonase RNA/DNA nuclease (25U/mL) was added per mL of extract. Beads and extract were left

O/N rotating in the cold room. Supernatant was collected and kept as a control of: Non Bound proteins. Beads were washed 3X with cold C-100* Buffer.

Elution - To elute, FLAG tripeptide (Sigma) was prepared at 0.2mg/mL. For each elution, 70 µl of FLAG tripeptide were added to the beads and left for 15 min at 4°C, mixing by taping the tube every 3-5 min. Five elutions were taken for each sample and collected in separate LoBind tubes. 5µl of every elution were transfer to new tubes to validate the presence of 3XFLAG OCT4 (WT and mutants) by Western Blot. For Sypro staining, 35µl of each elution were separated from one replicate. For MS, for each replicate 10 µl of the elutions (1-5) were pooled per replicate and processed by in-gel digestion.

SyproRuby staining of elutions - For one of the replicates, 35µL of each elution were taken for the gel. NuPAGE™ LDS Sample Buffer (4X) and Bolt 10X Reducing agent (10X) were added to each elution for a final concentration of 1X. Samples were heated at 70°C for 10 minutes. Final volume was loaded into a Bolt™ 4-12% Bis-Tris Plus Gel and ran at 200V for 30 min. After electrophoresis, gels were placed into a clean container with 100 mL of fix solution (50% methanol, 7% Acetic acid) and agitated on an orbital shaker for 30 minutes. Fix step was repeated once. After fixing, gels were washed for 10 min 3X with MiliQ. After washes, 50mL of SYPRO™ Ruby Protein Gel Stain were added and left overnight covered from light and in an orbital shaker. Next day, gels were transferred to a clean container and washed in 100 mL of wash solution (10% Methanol, 7% Acetic Acid) for 30 minutes. Before imaging gel was rinsed 2X in MiliQ. Gels were visualized using a UV Transiluminator.

SILAC

Protein extraction

After five passages with SILAC media, 10 cm dishes of hES and HF were scraped and pelleted by centrifuging for 5-10 minutes at 500 × g. Media was removed and cells were washed twice with PBS. Cells were lysed on ice using RIPA lysis buffer containing cOmplete Ultra Protease Inhibitor and sonicated on high with Bioruptor (6x10 sec intervals). Cell suspension was left for 15 minutes rotating in the cold room. Cells lysates were centrifuged for 15 minutes at max. speed (4°C) and transfer to protein LoBind tubes. Protein concentration was determined for each sample using the Pierce™ BCA Protein Assay Kit.

Coomassie staining - 5µg of each replicate (hES and HF) were separated by SDS-polyacrylamide gel electrophoresis in Bolt™ 4-12% Bis-Tris Plus Gel and stained with GelCode™ Blue Safe Protein Stain.

For MS analysis: Equal amount of protein was mixed for each replicate in a new tube. Samples were mixed as follows: hES1 + HF1 = hESHF R1, hES2 + HF3 = hESHF R2, hES3 + HF3 = hESHF R3.

2.2.10 Mass spectrometry

All protocols, materials and training were obtained from Christos Spanos in Juri Rappsilber lab (Wellcome Trust Centre for Cell Biology – Kings Buildings – The University of Edinburgh)

In gel digestion for MS - Used for the Immunoprecipitation protocol and SILAC

Gel: DTT was added to the IP and SILAC samples to a final concentration of 5%. NuPAGE™ LDS Sample Buffer (4X) was added to a final concentration of 2X. Samples were heated at 90°C for 10 min and let to cool before loading in the gel. Samples were loaded in a NuPAGE Novex 4-12% Bis-Tris gel and ran at 190V for 10-15 min, only to concentrate the samples at the top of the gel. Gel was washed with MiliQ for 5 min before staining with Instant™ Blue Coomassie for 1hr. Gel and Coomassie were washed 5x5 min with MiliQ before cutting.

Excise protein bands and Wash Coomassie stain: All these steps were done in a hood to avoid contaminants. For each sample, the piece of gel stained with Coomassie was cut into cubes ca. 1mm and transferred to microcentrifuge 1.5 mL tubes. Scalpel was washed with 70% EtOH between samples to avoid contamination from previous samples. To wash and remove Coomassie, 50mM Ammonium bicarbonate (ABC) was added to cover the gel pieces and incubated at room temperature for 5 min. ABC was discarded and 100% Acetonitrile (ACN) was added to cover gel pieces and incubated until the pieces became white and shrink. ABC and ACN washes were repeated twice. For the last wash, equal amount of ABC and ACN were added to cover the gel pieces and incubated for 1hr at 37^{o}C in a Thermostat with shaking until Coomassie was faintly blue. ACN was added until gel pieces were covered and incubated for 5 min. ACN was removed to Reduce and Alkylate.

Reduction/Alkylation: DTT solution (10mM DTT in 50mM ABC) was added to cover the gels and incubated for 30 min at 37^{o}C in a Thermostat. DTT solution was removed and ACN was added to cover the gels and incubated for 5 min to shrink the pieces. ACN was removed and Iodoacetamide (IAA) solution (55mM iodoacetamide in 50mM ABC) was added to cover the gel pieces and incubated for 20 min at RT in the dark (cover with foil). IAA solution was removed and gel pieces were washed with ABC for 5 min once prior to shrink with ACN for 5 min. ACN was removed prior to digestion.

Trypsin digestion: As described [188]. Trypsin buffer (13ng µL-1 trypsin in 10mM ammonium bicarbonate containing 10% (v/v) acetonitrile) was prepared as follows: 20 µL of 0.1% TFA (in 50mM ABC) was added to lyophilised Trypsin Protease (MS grade). Resuspended trypsin was transferred to a cold LoBind containing 1030 µL of dH_2O, 300 µL of 50mM ABC and 150 µL of ACN, trypsin was made fresh and kept in ice until use. Once prepared, trypsin buffer was added to the shrink gel pieces until covered. Gels with trypsin were incubated for 15 min at 4^{o}C. Tubes with gel pieces and trypsin were transferred to 37^{o}C in an incubator, after 30 min gel pieces were checked to see if all liquid was absorbed, if necessary, more trypsin buffer was added to completely cover the gel pieces. Samples were incubated overnight (12-16h) at 37^{o}C. Next day, digestion was stopped by acidifying the samples to pH < 2.5 with 10µ 10% Trifluoroacetic adic (TFA). Digested peptides were recovered by removing the supernatant liquid from the gel pieces and transferred to a LoBind tube before StageTip cleaning, this solution contained the peptides. To obtain more peptides from each sample, gel pieces were covered with 100% ACN for 5-10 min, until shrank. ACN was transferred into a clean LoBind tube and dried under vacuum centrifugation at 60 ^{o}C. 100 µL 0.1% TFA were added to the dried tubes to resuspend peptides and used for StageTip cleaning.

Stage tip cleaning – Used for all protocols: Digested peptides from ChIP-SICAP, SILAC and 3XFLAG-IP

As described by Rappsilber *et al.* [189]. Digested samples were acidified to a pH < 2.5 by adding 10-20µl with 10% Trifluoroacetic acid (TFA). Empore Disk C18 Octadecyl (C18)-bonded silica were manually cut and inserted into a pipette tip. Three disks were inserted in the tip for each sample. Before passing the digested samples, StageTips were washed by adding 50µL of methanol and centrifuged in a mini-table-centrifuge until all the liquid

passed through the disks. 70 µL of 80% Acetonitrile (ACN) in 0.1% TFA were added to the tips and centrifuged in a mini-table-centrifuge until all the liquid passed through the disks. To equilibrate StageTips in acidic conditions, 70µL of 0.1% TFA were added to the tips and centrifuged in a mini-table-centrifuge until all the liquid passed through the disks. Digested and acidified samples were added to the tips to bind the peptides to the disks. Tips were centrifuged in a mini-table-centrifuge until all the liquid passed through the disks. After passing all the digested sample, StageTips with the peptides bound to the disks were washed 2X with 100µL of 0.1% TFA and centrifuged in a mini-table-centrifuge until all the liquid passed through the disks. Tips can be left at -20°C for further analysis by LC-MS.

Mass Spectrometry – LC-MS – Steps performed by Christos Spanos in Juri Rappsilber lab (Wellcome Trust Centre for Cell Biology – Kings Buildings – The University of Edinburgh)

Peptides were eluted in 40 µL of 80% acetonitrile in 0.1% TFA and concentrated down to 1 µL by vacuum centrifugation (Concentrator 5301, Eppendorf, UK). Samples were then prepared for LC-MS/MS analysis by diluting them to 5 µL with 0.1% TFA. LC-MS-analyses were performed on an Orbitrap Fusion™ Lumos™ Tribrid™ (Thermo Fisher Scientific, UK) and on a Q Exactive mass spectrometers (both from Thermo Fisher Scientific) both coupled on-line, to Ultimate 3000 RSLCnano Systems (Dionex, Thermo Fisher Scientific, UK). In both approaches, peptides were separated on a 50 cm EASY-Spray column (Thermo Fisher Scientific, UK) assembled on an EASY-Spray source (Thermo Fisher Scientific, UK) and operated at a constant temperature of 50^{o}C. Mobile phase A consisted of 0.1% formic acid in water while mobile phase B consisted of 80% acetonitrile and 0.1% formic acid. Peptides were loaded onto the column at a flow rate of 0.3 µL min^{-1} and eluted at a flow rate of 0.25 µL min^{-1} according to the following gradient: 2 to 40% buffer B in 150 min, then to 95% in 11 min. For Orbitrap Lumos, survey scans were performed at 120,000 resolution (scan range 350-1500 m/z) with an ion target of 4.0e5. MS2 was performed in the Ion trap at rapid scan mode with ion target of 2.0E4 and higher-energy collisional dissociation (HCD) fragmentation with normalized collision energy of 27 (Olsen et al, 2007) . The isolation window in the quadrupole was set at 1.4 Thomson. Only ions with charge between 2 and 7 were selected for MS2. For Q Exactive, MS1 spectra were

recorded at 70,000 resolution and the top 10 most abundant peaks with charge ≥ 2 and isolation window of 2.0 Thomson were selected and also fragmented by HCD fragmentation of 27. The maximum ion injection time for the MS and MS2 scans was set to 20 and 60 ms respectively and the AGC target was set to 1 E6 for the MS scan and to 5 E4 for the MS2 scan. Dynamic exclusion was set to 6s.

Protein identification – Performed by Christos Spanos in Juri Rappsilber lab (Wellcome Trust Centre for Cell Biology – Kings Buildings – The University of Edinburgh)

The MaxQuant software platform [190] version 1.6.1.0 (released in April 2018) was used to process raw files and search was conducted against the complete/reference proteome of Homo sapiens (released in November, 2017), using the Andromeda search engine [191]. The first search peptide tolerance was set to 20 ppm while the main search peptide tolerance was set to 4.5 pm. Isotope mass tolerance was 2 ppm and maximum charge to 7. Maximum of two missed cleavages were allowed. Carbamidomethylation of cysteine was set as fixed modification. Oxidation of methionine and acetylation of the N-terminal were set as variable modifications. Label-free quantitation analysis was performed by employing the MaxLFQ algorithm as described by Cox et al [192]. SILAC quantification analysis was performed by employing the MaxQuant as described by Cox et al [193]. For peptide and protein identifications FDR was set to 1%.

2.2.11 DNA purification

Sonicated DNA

The 50µL of sonicated chromatin collected after sonication were reversed cross-linked in 150µL ChIP-Elution Buffer (50mM Tris-HCl pH8, 10mM EDTA, 1% SDS) by incubating for 16 hours at 65^{o}C in a shaker. Samples were then diluted with 200µL TE (10mM Tris-HCl pH8, 1mM EDTA) and incubated with 0.2mg/mL RNase A for 2 hours at 37^{o}C. Proteins were digested by incubating with 0.2mg/mL Proteinase K for 2 hours at 55^{o}C. The DNA was then purified by phenol-chloroform extraction followed by ethanol precipitation. Precipitated DNA was eluted in 50µL of 10mM Tris-HCl pH8.5 (EB buffer). DNA was quantified by NanoDrop and 2-3 µg of DNA were loaded in a 1.6% agarose gel with EtBr and ran at 60V for 3 hrs. Gels were visualised in an UV transiluminator.

DNA recovery for qPCR – ChIP-SICAP

To test DNA recovery via qPCR, hES and HF samples (FA XL and DSG+FA XL) were processed following the modified protocol ChIP-SICAP without following the protein digestion steps. To recover DNA for qPCR analysis, samples were processed after the streptavidin-capture by washing 5 times with RIPA Wash Buffer (50 mM HEPES-KOH, pH 7.5, 500 mM LiCl, 1 mM EDTA, 1% NP-40, 0.7% Na-deoxycholate) and once with TE NaCl (10mM Tris-HCl pH8, 1mM EDTA, 50mM NaCl). Bound chromatin was eluted by resuspending the beads in 200µL ChIP-Elution Buffer (50mM Tris-HCl pH8, 10mM EDTA, 1% SDS) and rocking at 65^{o}C for 30 minutes before transferring the supernatant to a new tube. Crosslinking was reversed by incubating for 16 hours at 65^{o}C. Samples were then diluted with 200µL TE (10mM Tris-HCl pH8, 1mM EDTA) and then incubated with 0.2mg/mL RNAse A for 2 hours at 37^{o}C. Proteins were digested by incubating with 0.2mg/mL Proteinase K for 2 hours at 55^{o}C. The DNA was then purified by Phenol:chloroform:Isoamyl extraction followed by ethanol precipitation. Precipitated DNA was eluted in 20µL of 10mM Tris-HCl pH8.5 for qPCR analysis. DNA was quantified by Qubit 2.0 using the HS dsDNA quantification kit.

ChIP-qPCR

DNA from ChIP (DSG+FA and FA) and ChIP-SICAP (original method) was amplified with PowerUp™ SYBR™ Green Master Mix as follows (LightCycler® 480 Roche II) 50^{o}C for 2 min and 95^{o}C for 2 min and then 45 cycles of 95^{o}C for 15 s and 60^{o}C for 1 min. Gene targets and oligonucleotides are in Table 2.3 . PCR specificity for each primer pair was measured by gel electrophoresis and melting curve analysis. Threshold cycle values (Ct) analysis were from three PCR replicates. qPCR results are normalised to Input DNA diluted to 1ng/µL and the enrichment of ChIP(FA XL and DSG+FA XL) and ChIP-SICAP DNA over input DNA was calculated by Enrichment=2$^{\wedge(-(\text{ct ChIP-ct input}))}$.

Table 2.3 Primers used for ChIP-qPCR

Name	Forward (5'-3')	Reverse (5'-3')
2MIR_367	ggaattagtgtaacattcctgcat	ctgctgtgagggcaaattaac
MYOD	ggacttatgtttgtatagcgggag	agaatagatttcctgccaagtg
2DPPA4_Prom	ggagattgagcactccttcag	ctgttgccacaagttccattatt
MIR_367_Neg	cctgggtaactgcactcaaa	gactacaggaatgtgccaact

2.2.12 ChIP-seq

ChIP – Modified from Soufi *et al.* [110]. OSKM 48 hrs (WT and mutants) were double cross-linked (DSG and FA), pelleted, lysed and sonicated as described in ChIP-SICAP (modified protocol). Samples were sonicated for 140 min for HF ctrl and OSKM 48h (WT and mutants). Sonication was done in 10 minutes intervals. Before ChIP, 50µl of sonicated chromatin were collected to test sonication quality in an agarose gel electrophoresis and to determine DNA concentration. Three IPs were performed per OCT4 (WT and mutants) using 40µg of sonicated chromatin per IP. All buffers should be fresh and cold and all tubes should be LoBind. For each IP 35µl of Dyna G Magnetic Beads were transferred to a Prechill LoBind tube and washed 3X with 1mL of Blocking buffer (0.5 BSA in PBS). Beads were resuspended in 800 µl of Blocking buffer with 10µg of OCT4 ab per IP and incubated for 6 hr (minimum) on a rotating platform at 4°C. Beads were washed 3X in 1mL of blocking solution and resuspended in 100µl LB3 (see ChIP-SICAP) buffer. 40 µg of sonicated chromatin were added to each IP and volume was top up to 900 µl using LB3 buffer and protease inhibitors. IPs were incubated overnight in a rotator platform at 4°C. Next steps were done in the cold room. Using the magnetic rack to separate beads, supernatant was transferred to a pre-chill LoBind tube, supernatant is the no bound fraction. Beads were washed 4X with cold RIPA-wash buffer (50 mM Hepes-KOH pH 7.6, 500 mM LiCl, 1 mM EDTA, 1% NP-40, 0.7% Na-Deoxycholate). Beads were washed 1X with TE+NaCl(10mM Tris-HCl pH 8, 1mM EDTA pH 8 and 50mM NaCl), followed by a spin at 300 x g for 3 minutes at 4°C and to remove any residual TE buffer. 210 µL of ChIP elution buffer (see ChIP-SICAP) were added to be beads and let at 65°C for 30 minutes shaking at 1200rpm to elute the proteins and DNA. Tubes were centrifuged at 16,000 x g for 1 minute at room temperature and 200 µL of supernatant was transferred to a new tube. In parallel, 50 µL of sonicated chromatin from the INPUT after sonication was thawed before adding 150 µL of ChIP elution buffer. ChIPs and input were reverse cross-linked by incubating at 65°C overnight (shake 700rpm).

Digestion of Protein and RNA: An equal volume (200 µL) of TE (10mM Tris-HCl pH8, 1mM EDTA) and incubated with 0.2mg/mL RNAse A for 2 hours at 37^{o}C. Proteins were digested by incubating with 0.2mg/mL Proteinase K for 2 hours at 55^{o}C. To extract DNA, 400 µL Phenol:chloroform:isoamyl alcohol were added to the samples to separate phases by spinning the sample at top speed for 5 min. The aqueous layer was transferred to a new

tube 16 µL of 5M NaCl (200 mM final concentration) and 1.5 µL of 20 µg/µL glycogen (30 µg total). DNA precipitation was performed by adding 0.8mL of cold 100% EtOH and incubated for 180 min at least at -20°C. Tubes were centrifuged 20,000 x g for 10 minutes at 4°C to pellet DNA. Supernatant was carefully decanted taking care of the pellet, which were washed with 500 µL of 80% EtOH spin at 20,000 x g for 10 minutes at 4°C to pellet DNA after each wash. Supernatant was removed by pipetting and pellets were allowed to dry for 5 min. Each pellet was resuspended in 20 µL MiniPrep Elution buffer (10mM Tris-HCl pH8.5, Qiagen) using a P20 pipette. DNA was quantified by Qubit 2.0 using the HS dsDNA quantification kit.

Sequencing Library Generation

Libraries were prepared from ChIP-DNA pooled using equal volumes of 3 replicates ChIP for each OCT4 (WT and mutant) using the NEBNext Ultra II Library Preparation Kit with Dual Index Primers with size selection for fragments of approximately 200bp carried out using SpeedBeads™, which comprise magnetic carboxylate modified particles. For each OCT4 (WT and mutants), libraries were prepared using 20-50ng ChIP DNA. Input libraries were generated using 20ng of sonicated DNA. PCR amplification during library preparation was limited such that samples underwent 10 cycles of PCR amplification. Libraries were quantified using a Qubit 2.0 device with a high sensitivity dsDNA kit and fragment size was determined using an Agilent 2200 Tapestation with D1000 HS reagents. The DNA libraries were then pooled by mixing an equal concentration of each ChIP DNA library. The concentration of the ChIP DNA library pool was determined to be 24.8 nM by an Agilent 2200 Tapestation with D1000 HS reagents. Library was submitted for sequencing using a NovaSeq S1 50PE (1 lane) platform to yield approximately 750M + 750M paired ends. Sequencing was performed by Edinburgh Genomics (Kings Buildings, The University of Edinburgh).

2.2.13 Cloning

All plasmids (donated, bought and new constructs) were verified by sequencing

Plasmids

OSKM 48h: pwPT-GFP, pwPT-rtTA2M2, psPAX2, pMDG and the FU-tetO-O/S/K/M vectors were obtained from Abdenour Soufi. FU-tetO-OCT4 plasmid mutants (O lin-min, O lin29-

42 and O lin97-119) were obtained from Burak Özkan (Soufi lab).

Rescue assays: CAG-IP-3XFLAG-mOct4, CAG-IP-GFP and CAG-IP-empty plasmids for rescue assays were obtained from Chambers Lab.

sgRNA KO: pKLV2-U6gRNA5(BbsI)-sEF1aBFP-W (KPL474) backbone for sgRNA was obtained already linearized from Benedetta Carbone (Keisuke Kaji Lab). Zeo, Tpr53 and Dot1L cloned vectors were donated by Dan K (Kaji Lab) and Stat3 cloned vector was donated by Meryam B (Kaji Lab)

Overexpression of candidates: Plasmids with coding sequences for UFD1L (HsCD00324735, human), ETV4 (HsCD00326736, human), XPO6 (HsCD00418235, human) and RAI1 (HsCD00329661, human) were bought from Harvard PlasmID Repository (DNA Resource Core, Harvard Medical School). Plasmid for Mcmbp (NM_145955, Mouse Tagged ORF Clone, CAT#: MR209710) was bought from OriGene. Plasmid for TNIP2 (cDNA ORF Clone in Cloning Vector, Human, Cat: HG19965-U) was bought from Sino Biological. FU-tetO-ZBTB2 was donated by Dan K (Kaji Lab). Plasmid for KDM4B was donated by Tülin Tatar (Kristian Helin lab).

FU-TET-O cloning

3XFLAG-OCT4 (WT)

To construct the FU-tetO-3XF-OCT4 the 3XFLAG tag sequence was added to the N-terminus of OCT4 using as a template the 3XFLAG sequence from CAG-IP-3XFLAG-mOct4 plasmid obtained from Nick Mullin (Chambers Lab). PCR product was digested with BsmBI and SfiI and ligated with T4 DNA Ligase into FU-tet-O-hOCT4 plasmid linearized with BsmBI and SfiI. Primers are listed in Table 2.4.

3XFLAG-OCT4 Mutants

To construct FU-tetO-3XF-O lin-min/lin29-42/lin95-117 the 3XFLAG tag sequence was added to the N-terminus of each factor using as a template the sequence from FU-tetO-hO lin-min/lin29-42/lin95-117 plasmids obtained from Burak Özkan (Soufi lab). PCR products were inserted into FU-tet-O-3XF-hOCT4 plasmid linearized with BamHI and XbaI

using the In-Fusion® HD Cloning Kit. Primers are listed in Table 2.4.

Candidates

To construct FU-tetO-UFD1L/XPO6/MCMBP/RAI1/TNIP2/ETV4/KDM4B, PCR products were inserted into FU-tetO plasmid linearized with EcoRI and XbaI using the In-Fusion® HD Cloning Kit. Primers are listed in Table 2.4.

Table 2.4 Primers used for FU-tetO Cloning

Construct made	Template	Primers (5'-3')	Enzymes
FU-tetO-3XF-hOCT4	CAG-IP-3XFLAG-mOCT4	Fwd_3XFLAG_hOCT4 agatcgcctggagacgccatccacgctgtcaacgtgctggttgttgt	BsmBI
		Rvs_3XFLAG_hOCT4 ggctccggccccctggcccatcacctccaccacctggagggggcgaga aggcaaaatctgaagccaggtgtcccgccat	SfiI
FU-tetO-3XF-hOCT4 (mutants)	FU-tetO-hOCT4 (mutants)	BamHI_3FOCT4 cgacgacaagggatccggcggcggcggcggcgccatggcgggac	BamHI
		XbaI_FS_OCT4 gcttgatatctctagtcagtttgaatgcatgggagagct	XbaI
FU-tetO-UFD1L	pOTB7-UFD1L	UFDL1_fwd_EcoRI ccgcggccccgaattcgccaccatgttctctttcaacatg	EcoRI
		UFDL1_rvs_XbaI gcttgatatctctagattagggctttcttccctttttacgc	XbaI
FU-tetO-RAI1	pOTB7- RAI1	RAI1_fwd_EcoRI ccgcggccccgaattcgccaccatgcagtcttttcga	EcoRI
		RAI1_rvs_XbaI2 gcttgatatctctagacaggaaacagctatgaccatgtgc	XbaI
FU-tetO-MCMBP	pCMV6-MCMBP	Mcmbp_Fwd_EcoRI ccgcggccccgaattcgccaccatgccctgtgga	EcoRI
		Mcmbp_Rvs_XbaI_MycFlag gcttgatatctctagattaaaccttatcgtcgtcatccttg Mcmbp_Rvs_XbaI gcttgatatctctagattaaagctcgttcccattcacact	XbaI
FU-tetO-XPO6	pLX304-XPO6	XPO6_fwd_EcoRI ccgcggccccgaattcgccaccatggcgtcagtt	EcoRI
		XPO6_rvs_XbaI gcttgatatctctagactacgtagaatcgagaccgagga	XbaI
FU-tetO-TNIP2	pUC19-TNIP2	TNIP2_EcoRI_fwd ccgcggccccgaattcgccaccatgtcccgggacc	EcoRI
		TNIP2_XbaI_rvs gcttgatatctctagatcactggcagcactcggc	XbaI
FU-tetO-ETV4	pCMV-SPORT6-ETV4	ETV4_fwd_EcoRI ccgcggccccgaattcgccaccatggagcggagg	EcoRI
		ETV4_rvs_XbaI gcttgatatctctagactagtaagagtagccacccttggg	XbaI
FU-tetO-KDM4B	pCMV-HA-JMJD2B	KMBD4_fwd_EcoRI ccgcggccccgaattcgccaccatggcatacccatacg	EcoRI
		KMDB4_rvs_XbaI gcttgatatctctagactagaagggggctccggg	XbaI

sgRNA cloning

To construct the sgRNA lentivirus, sgRNA sequences were obtained from a mouse reported library [194]. Primers were order as 19-bp complementary oligonucleotides with the following 5' and 3' attachments for cloning:

- Top strand: Add "CACCG" to the 5' end.
- Bottom strand: reverse complement the sequence and add "C" at the 3' end and "AAAC" to the 5' end.

Oligos were annealed using a heat block starting at 95 °C and allowed to cool slowly over 12 min to RT. Annealed oligos were diluted to 7.1 pmol/µL. sgRNA lentivirus vector (pKLV2-U6gRNA5(BbsI)-sEF1aBFP-W (KPL474)) was digested with BbsI and donated by Benedetta C. 20ng of linearized vector and 2µL of diluted annealed oligos were ligated T4 DNA ligase. Oligos are listed in Table 2.5.

Table 2.5 Oligos used for sgRNA lentivirus cloning

sgRNA	Oligos (5'-3')
Rai1	RAI1_fwd caccgcatcggcctatcatgaggc
	RAI1_rvs aaacgcctcatgataggccgatgc
Tnip2	TNIP2_fwd caccggatgaacgacagtgtgcac
	TNIP2_rvs aaacgtgcacactgtcgttcatcc
Ufd1l	UFD1L_fwd caccgggatacaccgctttagggt
	UFD1L_rvs aaacaccctaaagcggtgtatccc
Xpo6_1	XPO6_1_fwd caccgcggtacttacgccagagct
	XPO6_1_rvs aaacagctctggcgtaagtaccgc
Xpo6_2	XPO6_2_fwd caccgtcatcttacatcgtcgtcc
	XPO6_2_rvs aaacggacgacgatgtaagatgac
Mcmbp	MCMBP_fwd caccgtactgtgtccccgtgcccg
	MCMBP_rvs aaaccgggcacggggacacagtac
Fbrsl1	FBRSL1_fwd caccgcgttggaatgtcggaagta
	FBRSL1_rvs aaactacttccgacattccaacgc
Etv4	ETV4_fwd caccgcaccaaggtacccgtggcc

	ETV4_rvs aaacggccacgggtaccttggtgc
Etv5	ETV5_fwd caccgaggacccacccctttgaact
	ETV5_rvs aaacagttcaaggggtgggtcctc
Kdm4b_1	KDM4B_1_fwd caccgtggcgtacattgagtcgca
	KDM4B_1_rvs aaactgcgactcaatgtacgccac
Kdm4b_2	KDM4B_2_fwd caccgtgtcatcatacgtctgccg
	KDM4B_2_rvs aaaccggcagacgtatgatgacac

CAG-IP cloning

To construct the CAG-IP-hOCT4/3XFLAGhOCT4 the hOCT4 and 3XFhOCT4 sequences were obtained from FU-tetO-hOCT4/3XFhOCT4. PCR products were digested and ligated with T4 DNA Ligase into CAG-IP plasmid linearized with NotI and dephosphorylated with Shrimp Alkaline Phosphatase (rSAP). Primers are listed in Table 2.6.

Table 2.6 Primers used for CAG-IP Cloning

Construct made	Template	Primers (5'-3')	Enzymes
CAG-IP-hOCT4	FU-tetO-OCT4	pCAG_Oct4NotI_fwd aattcgcggccgcgagacgccatccacg	NotI
		pCAG_Oct4NotI_rvs gaggggtctagaggcgccgccgccgccgccgg	NotI
CAG-IP-3XFhOCT4	FU-tetO-3XFOCT4	pCAG_3XFOct4NotI_fwd aattcgcggccgccaacgtgctggttgttgt	NotI
		pCAG_Oct4NotI_rvs atcgagcggccgctcagtttgaatgcat	NotI

2.2.14 Data Analysis

Mass spectrometry

Filter against Controls

To define the identified proteins for each sample, datasets were filter against their respective controls, using the Perseus Software [195]. First, datasets were processed and filtered out against 'Reverse' and 'Only identified by site' proteins, followed by filtering against contaminants. Then, proteins only identified by one peptide sequence were discarded, using minimum two peptides as the cut-off value. LFQ values were transformed to log2(x). Missing values were imputed using the minimum value setting.

To define identified properties, each condition was compared against its respective control. ChIP-SICAP datasets: OSKM 48h (WT and mutants) were analysed against HF control (no OSKM and OCT4 ab) and hES was filtered against hES control (hES and IgG ab). 3XFLAGIPs: 3XFOSKM (WT and mutants) were filtered against HF control (No OSKM and IPed with 3XFLAG beads). t-test was performed for each comparison using a FDR of 0.1 as a threshold value and considering 1.5 fold change as the differentially enriched cut-off value.

Differential Enrichment Analysis hES vs OSKM 48h

Identified proteins for OCT4 ChIP-SICAP in hES and OSKM 48h filtered against control were analysed using the Perseus software [195]. LFQ values were transformed to log2(x). Missing values were imputed using the minimum value setting. To define differentially enriched properties a two sided t-test was performed with 250 randomizations and a FDR of 0.1 as a threshold value and considering 1.5 fold change as the differentially enriched cut-off value. To visualize the data a volcano plot was generated, choosing the t-test difference (Fold change) for the x- and the –log t-test p-value for the y-axis.

Cytoscape network

Networks of ChIP-SICAP identified proteins for hES and OSKM 48h was built and analysed using Cytoscape [196]. First separate networks for hES and OSKM were created using the STRING app for Cytoscape [197]. To create each network the reported interactions between the list of identified proteins for each dataset were looked in the literature using the *Homo sapiens* database establishing a confidence (score) cut-off of 0.7. Both networks were overlapped and visualised using the DyNet Analyser app [198] for Cytoscape and using the fold change values defined in the differential enrichment Analysis in Perseus (previous section) for the nodes colouring.

Heatmaps and individual protein profiles ChIP-SICAP and 3XFLAG IP

Hierarchical clustering heatmaps, PCA plots and individual protein profiles for ChIP-SICAP and 3XFLAG-IP analysis were performed using the R [199] package DEP (Differential Enrichment analysis of Proteomic Data) [200]. For each analysis, a file containing all the identified proteins (filtered against controls) for each sample and their respective LFQ

values was created. LFQ values were transformed to log2(x). Missing values were imputed using the function minimum value setting in the command *impute(data_se1, fun = "min").* PCA plots were created with the function *plot_pca.* To define differentially enriched properties a Differential enrichment analysis based on linear models and empherical Bayes statistics was performed using the command *test_diff (imputed_data, type = "all")*, where "all" indicates individual comparison of all conditions against each other. To define the significant changes the command *add_rejections(alpha=0.1, lfc=1)* was used, where alpha is the adjusted pvalue and lfc is the fold change (=2 fold). Hierarchical clustering heatmaps were created with *plot_heatmap.* Individual protein profiles were created with the function *plot_single.*

SILAC Statistical analysis

SILAC data was analysed with Perseus software [195]. First, datasets were processed and filtered out against 'Reverse' and 'Only identified by site' proteins, followed by filtering against contaminants. Proteins only identified by one peptide sequence were discarded, using minimum two peptides as the cut-off value. Proteins only present in one replicate were discarded, and only proteins present in two out of the three replicates were taken into account. The ratios HF/hES were used to define proteins significantly different between HF and hES. A one-sample t-test was performed defining the cuttoffs: p-value <0.05 as significant and fold change ≤ -1 or ≥ 1 (= 2-fold change). To visualize the data a volcano plot was generated, choosing the t-test difference (fold change) for the x- and the –log t-test p-value for the y-axis.

Heatmaps SILAC and Microarray Data

HF/hES SILAC ratios and RNA levels of the proteins identified in ChIP-SICAP hES and OSKM were subtracted from the respective datasets to generate the heatmaps using the R [199] package *gplots* and the function *heatmap.2* [201].

Protein Enrichment

For all proteomic data, to define Gene Ontologies enrichment, Panther classification system was used [202]. To enrich for pathways and Complexes, ConcensusPathDB database was used [203].

ChIP-seq – Analysis was done with the help of Abdenour Soufi

Mapping of sequenced reads

The quality of the next generation sequencing (NGS) raw data (FASTQ files) was measured by FASTQC tool. All samples scored QC values of more than 30 passing the quality control standard for NGS data. The pair-end sequences were mapped to the *Homo sapiens* genome assembly GRCh37 (hg19) using Bowtie (version 2.3.4.1) [204] and very sensitive parameters. Duplicated reads were then removed using MarkDuplicates from the Picard toolkit (http://broadinstitute.github.io/picard/) and resulting bam files were indexed using the index tool from SamTools [205]. The sequencing coverage and the insert size distribution were measured from the resulting bam files using Qualimap (version 2.2.1)[206]. Overall alignment rate was more than 95% in all samples (hESCs= 95.23%, O WT=98.17%, O lin-min= 97.13%, O lin95-117= 97.75%, O lin29-42= 95.6%, HF input =96.90%). Average insert size distribution was 200bp (hESCs= 218, O WT=224, O lin-min= 212, O lin95-117= 202, O lin29-42= 162, HF input =186).

Peak calling

The indexed aligned reads with no duplicates (bam files) were used for peak-calling. Peaks of OCT4 in hES and OSKM 48h (WT and mutants) showing a significant enrichment over input DNA were called using MACS2 (version 2.1.1.20160309) [207] and a fragment size of 200 bp and were controlled to q-value (minimum FDR) cut-off of 0.01. Peaks were extended to 300bp by first finding the summit using awk and then extending using the slop tool from DeepTools [208] adding 150bp to each side of the summit. The peaks that overlapped with the human ENCODE blacklist were removed. Input signal was subtracted using the bedmap tool from BedOps [209] and bed files were sorted according to the intensity of the peaks.

Coverage track and normalization

The indexed aligned reads with no duplicates (bam files) were normalised for sequencing coverage to 1X genome depth (reads per genome coverage, RPGC) using the bamCoverage tool from DeepTools and a bin size of 10 bp and extendReads parameters [208]. Reads within the human ENCODE blacklist were removed from the analysis. The

resulting bigwig files were converted to wig format using the bigwigtowig tool, which were then converted to bed files using the wigtobed tool [210].

Interactive genome visualization

The bigwig files and the peaks files were used to visualize the coverage track and the called peaks for each OSKM 48h sample (WT and mutants) along the *Homo sapiens* genome assembly GRCh37 (hg19) using the Integrative Genomics Viewer Java Application [211].

Genomic intersections

To identify unique and shared peaks between samples, all peak files were integrated into a single file using the tool everything from BedOps [209]. Then, the peaks of the integrated file were overlapped using the tool merge from BedTools [209]. This tool integrates a final column that indicates from which sample or samples, the identified peak originally came from. For unique peaks this column would only contain the name of one sample. For shared peaks the column will contain the combination of samples the peak was identified in. To extract the files for the unique and shared peaks the function awk was used, generating individual bed files the unique peaks for each sample and the shared peaks between different combinations of samples. The bed files were then ranked by the intensities of the peaks. The intersection between peaks mutants was carried out using the Intervene UpSet tool [212].

Read density maps

To generate the read density heatmap, a density matrix was first computed using the DeepTools [208] tool computeMatrix reference-point and the following parameters; --referencePoint center, --binsize 10, -b 1000 -a 1000, --sortregions keep, and --averageTypeBins sum . For the hES vs OSKM48hrs read density heatmap, the reference files (-R) were the bed sorted files of the unique peaks for each condition and the bed sorted file for the shared peaks between both, while the score files (-S) consisted in the normalised ChIP-seq bigwig files of hESCs and OSKM 48h total peaks. For the OSKM 48h (OCT4 WT and mutants) density heatmap, the reference files (-R) were the bed sorted files of the unique peaks for each OCT4 (WT and mutants) and all the possible

combinations of shared peaks bed sorted files, while the score files (-S) consisted in the normalised ChIP-seq bigwig files of each individual condition total peaks CITE. For both cases, the analysis excluded the ENCODE blacklist. The resulting matrix files were then used to generate the heatmaps and profile plots using the DeepTools CITE tool plotHeatmap [208].

Motif analysis

For each bed file of unique and shared peaks, *de novo* motif analysis was carried out using the MEME suite installed in a local LINUX server [213]. First, the DNA sequences (FASTA) were extracted from the central 200 bp of the ChIP-seq peak regions using the BedTools getfasta tool [208]. To use as background, DNA sequences (200 bp) were extracted from genomic regions located 1 Kb upstream from the summit of each peak. All regions were filtered through the human ENCODE blacklist. Second, the 1st-order Markov background model was generated using the fasta-get-markov tool. Finally, meme-chip was run using the Fasta sequence files and the corresponding Markov model and the following parameters; -nmeme 600, -meme-mod zoops, -meme-minw 6, -meme-maxw 18, -meme-maxsize 50000000, -dreme-e 0.00001, -dreme-m 20 using the JASPAR core motif database [214]. The most enriched de novo motifs discovered by DREME were analysed by CentriMO to confirm their central enrichment over the background sequences and compared to the canonical motifs using Tomtom. Motif central enrichment were carried out using the CentriMo tool [215].

Distribution of sites in the genome

GREAT Tool (http://great.stanford.edu/public/html/index.php) [216] was used to determine the distribution of unique and shared OCT4 (WT and mutants) bound sites with respect to transcription start sites (TSS) of Refseq genes. Sorted bed files of unique and shared binding sites were analysed separately and combined in a distribution graph.

Chapter 3 OCT4 ENGAGEMENT WITH CHROMATIN-ASSOCIATED PROTEINS DURING PLURIPOTENCY MAINTENANCE AND EARLY REPROGRAMMING

3.1 Introduction

The overexpression of a set of transcription factors can revert differentiated somatic cells into a pluripotent state. Among these factors is member of the POU transcription factor family OCT4 that, in combination with SOX2, KLF4 and c-MYC lies at the centre of the transcription factor network that is fundamental for the pluripotency maintenance in ES cells. While OCT4 can efficiently maintain pluripotency in ESCs, the reprogramming capacity of OCT4 is highly inefficient and often result in partially reprogrammed cells [84]. It is therefore important to understand how OCT4 can regulate pluripotency in these diverse cellular contexts.

As a main factor in both, pluripotency maintenance and reprogramming, different studies have been focused in understanding its mechanisms and properties in each process. In ES cells, OCT4 mainly functions through the activation of pluripotency maintenance-associated and self-renewal-associated genes, while simultaneously repressing genes that promote differentiation [217]. During early stages of reprogramming OCT4 acts as a pioneer transcription factor, targeting silenced pluripotency as well as non-pluripotency genes within closed chromatin for subsequent activation [110].

In both reprogramming and pluripotency maintenance, OCT4 interaction with chromatin and other proteins is fundamental to regulate gene expression and cell fate decisions. The interaction of OCT4 with the transcription factors SOX2 and NANOG define the core pluripotency maintenance network that maintains pluripotency [82]. In addition, it is well known that interactions with chromatin regulators, other transcription factors and the transcription machinery, also modulate OCT4 function in ESCs [82, 84, 163, 172, 178]. Yet, the identification of these OCT4 partners has been largely studied in mouse ESCs, revealing key insights of OCT4 function during pluripotency maintenance. However, the interactions of OCT4 with other proteins, specifically those associated with chromatin

during are yet to be defined. Because of their importance for a successful reprogramming and for pluripotency maintenance, the identification of these OCT4 chromatin-dependent interactions could provide a better understanding of the protein complexes necessary for the chromatin dynamics and the reshaping of the chromatin landscape of the genome in the induction and pluripotency maintenance, particularly in the poorly-studied human system.

3.1.1 ChIP-SICAP as a tool for the identification of chromatin-associated partners

Several methodologies for affinity enrichment and analysis of chromatin-associated complexes have been developed. The principle of most of these approaches relies on the enrichment of specific chromatin components by chromatin immunoprecipitation protocols (ChIP) followed by protein identification using mass spectrometry (MS). These approaches include modified ChIP, ChIP-MS and rapid immunoprecipitation mass spectrometry of endogenous protein (RIME) [218]. A common disadvantage of these approaches is the lack of discrimination between direct and non-direct interactions, in addition to high protein background of non-specifically associated proteins with the antibody and other reagents.

To overcome these limitations one of the most recent methods termed selective isolation of chromatin-associated proteins (ChIP-SICAP) takes advantage of a classic ChIP followed by DNA-labelling and an extra purification step, allowing the specific capture of only protein-DNA complexes in the direct vicinity of the bait protein on a short stretches of DNA (Fig. 3.1) [219]. In ChIP-SICAP, cells are treated with formaldehyde as in a standard ChIP method to crosslink proteins that are in direct contact with DNA, allowing the immunoprecipitation of specific protein-DNA complexes along with all proximally bound proteins. The 3'-end labelling of DNA fragments with biotinylated nucleotides using a terminal deoxynucleotidyl transferase (TdT), followed by denaturation allows the disruption of all non-cross-linked proteins and the antibody, which helps to get rid of background noise and of the antibody contamination. The isolation of DNA-protein complexes using streptavidin-beads, with further stringent washes helps capture the purified biotinylated DNA in complex with directly interacting proteins. In the final step,

DNA-protein complexes are reverse cross-linked, the digested peptides are identified by MS and DNA subjected to high-throughput sequencing (Fig. 3.1) [179].

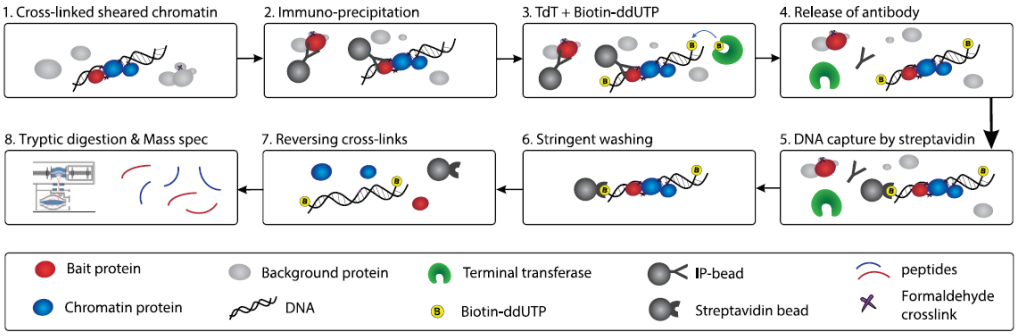


Fig. 3.1 ChIP-SICAP Workflow. Diagram representing the fundamental steps of ChIP-SICAP protocol. DNA proteins are cross-linked and sonicated. Chromatin is then immunoprecipitation with a suitable antibody following biotinylation of DNA for its retrieval along with interacting proteins on streptavidin beads. Extensive washes are applied before the isolation of chromatin fragments for reverse cross-linking. Lastly, proteins are digested and identified by mass spectrometry. Image taken from [179].

ChIP-SICAP benefits were demonstrated as an important tool for the expansion of the pluripotency maintenance network in mouse embryonic stem cells (mESCs), proving that this method is a powerful tool to gain a better understanding of transcriptional networks in general, and in pluripotency maintenance. Therefore, ChIP-SICAP represents a useful tool to be applied for the better understanding of human chromatin associated networks. More specifically, it can be used to describe for the first time the chromatin-associated protein networks that define pluripotency and the reprogramming process in the human context, which is a field that has not been yet addressed.

3.2 Aims of this chapter

- Identify the OCT4 chromatin-associated proteins in human ESCs and in early reprogramming of human fibroblasts.
- Compare and contrast the OCT4 interactomes in pluripotency and early reprogramming.
- Quantify the levels of proteins identified as partners of OCT4 in hESCs and early reprogramming.

3.3 Results

The results of this chapter are presented in four different sections. First, the ChIP-SICAP protocol was modified to identify OCT4 chromatin associated proteins in human embryonic stem cells (hESCs). Once modified, the protocol was applied to identify OCT4 chromatin associated proteins at early stages of reprogramming (48 hrs after OSKM induction). Next, both OCT4 interactomes, in hESCs and early reprogramming, were compared to define the similarities and differences between OCT4 associated chromatins during pluripotency maintenance and early reprogramming. Lastly, quantitative proteomics was performed in human fibroblasts and embryonic stem cells to investigate the protein levels of the different proteins identified by ChIP-SICAP.

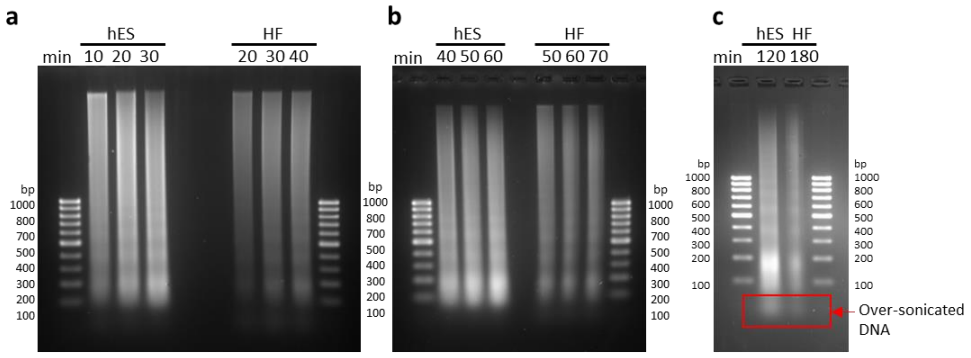
3.3.1 Modification of ChIP-SICAP for the identification of OCT4 chromatin-associated protein in human pluripotency

ChIP-SICAP allows the simultaneous identification of protein and DNA interactions [179], therefore it was employed to define OCT4 chromatin-associated partners in human ESCs and the early reprogramming of human fibroblasts 48 hours after inducing: OCT4, SOX2, KLF4 and cMYC (OSKM 48h).OCT4 ChIP-SICAP was initially tested in hES cells using human fibroblasts (HF) with no OSKM expression as a negative control. hES cells were grown in feeder-free conditions and defined media, eliminating contaminant proteins from feeder cells.

Following the original ChIP-SICAP protocol (Fig. 3.1) (Section 2.2.9 in Materials and Methods) [179], 24 million cells were collected and pelleted from both conditions for further crosslinking with formaldehyde. Chromatin fragmentation was optimized by testing various sonication times at 10 minutes intervals and measuring the length of DNA fragments (Fig. 3.2a-b). Despite testing extensive sonication times, 2 hours for hES and 3 hours for HF, the resulting DNA fragments sizes remained sub-optimal since the required DNA fragments (between 100 and 300 bp) were not predominantly enriched (Fig. 3.2c). These results could indicate that the cross-link, protein purification and DNA purification protocols reported in the original ChIP-SICAP method might not be the optimal conditions for the sonication of fibroblasts and hES used in this thesis but the lack of a reference image of the sonicated DNA used in the reported protocol was not provided

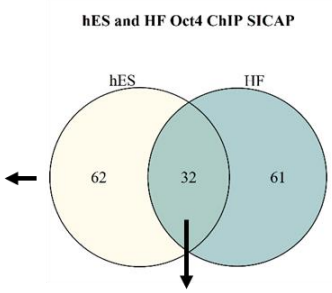
for comparison. Further sonication was not followed as over-sonicated fragments started to appear in the samples (Fig. 3.2c red box). Despite the sonication was not ideal, the next steps of the protocol were tested and followed as originally described (see Section 2.2.9 in Materials and Methods). Digested and purified peptides were processed by liquid chromatography-mass spectrometry (LC-MS) and were identified by Mascot software against the UniProt human database. Only a small number of proteins were identified from both samples: 94 for hESCs and 93 for HF, showing a significant overlap 32 proteins (Fig. 3.2d). Most of the identified proteins had a low number of peptide matches, with high presence of keratin and common proteomic contaminants. For hES, the bait OCT4 was identified with a low rank and only one peptide match (Fig. 3.2d). Altogether, this indicated poor protein recovery and hence not suitable for identifying OCT4 protein partners.

Due to the lack of protein recovery, the original protocol was modified and modified to increase the efficiency of both protein and DNA recovery (Fig. 3.3a) (Section 2.2.9 in Material and Methods). First, an additional cross-linking step was used. For standard ChIP-seq, one-step cross-linking with formaldehyde (FA) is routinely employed to study protein-DNA interactions. FA is a zero-length cross-linker making it ideal for the cross-linking of direct and close DNA-proteins interactions. However, this also limits its functionality for protein-protein interactions usually present in chromatin complexes not-directly associated with DNA. To stabilize OCT4 protein complexes, an additional disuccinimidyl glutarate (DSG) cross-linking was used. DSG is an irreversible membrane permeable amine-reactive cross-linking agent that cross-links NHS esters with an effective radius of 7Å, stabilizing protein-protein complexes [220]. This additional cross link will capture OCT4 chromatin partners that might not be directly interacting with DNA and therefore not cross-linked with formaldehyde. This two-step cross-linking protocol using DSG in combination with FA has been previously used for ChIP-seq analysis of transcription factors, polymerases, co-activators and histones [221]. By combining the DSG cross-link with a previously reported OCT4 ChIP-seq protocol [110], the new two-step cross-link protocol was successful in improving the fragmented chromatin recovery (100-300bp) in hES, as well as reduced the sonication time from two hours to 90 minutes, as shown in Fig. 3.3b.



d

RANK	PEPTIDES	ID
5	5	MATR3
9	3	HNRNPK
10	4	KRT8
11	5	HSPA8
13	1	HNRNPA2B1
16	1	TUBB4A
17	1	TUBB3
19	4	ACTG1
20	1	HNRNPL
21	2	CCAR2
23	1	LRRC47
25	1	CCT2
27	2	NCL
28	1	MCM7
29	2	KRT17
31	2	RBBP4
33	1	SRSF1
34	1	LIN28A
35	1	TMPO
36	**1**	**POU5F1**



RANK	PEPTIDES	ID
1	17	KRT1
2	10	KRT10
3	4	HSP90AB1
4	5	KRT9
6	7	KRT5
7	7	KRT6A
8	3	KRT2
12	1	PRKDC
14	2	RPL3
15	3	HNRNPA3
18	2	SND1
22	3	MYH9

Fig. 3.2 OCT4 Original ChIP-SICAP protocol in hES and HF. Agarose gels with DNA purified from sonicated chromatin. a. First round of sonication: 10, 20 and 30 min for hES and 20, 30 and 40 min for HF Control. b. Second round of sonication: 40, 50 and 60 min for hES and 50, 60, and 70 min for HF. c. Final sonication times: 120 min for hES and 180 for HF. d. Venn diagram showing the total number and intersection of identified proteins for hES and HF OCT4 ChIP-SICAP. Tables indicate the proteins identified with their respective ranking and peptide match.

To test the performance of the adapted protocol in DNA recovery and whether the double cross-linking had an effect in the background signal; DNA was purified after the streptavidin immunoprecipitation (before protein digestion) from both the original and modified methods and analysed by qPCR. Two positive regions known to be occupied by OCT4 in hESCs (MIR367 and DPPA4) and two negative regions with no occupancy (MIRNEG and MYOD) were used [110, 222]. Both OCT4 positive sites showed significantly

more enrichment over the input in the samples that were cross-linked with both DSG and FA, in comparison with the original ChIP-SICAP protocol using FA only fixation. In addition, there was no significant increase in the enrichment of the OCT4-negative sites, indicating that the additional DSG cross-link had no effect in on the background signal (Fig. 3.3c).

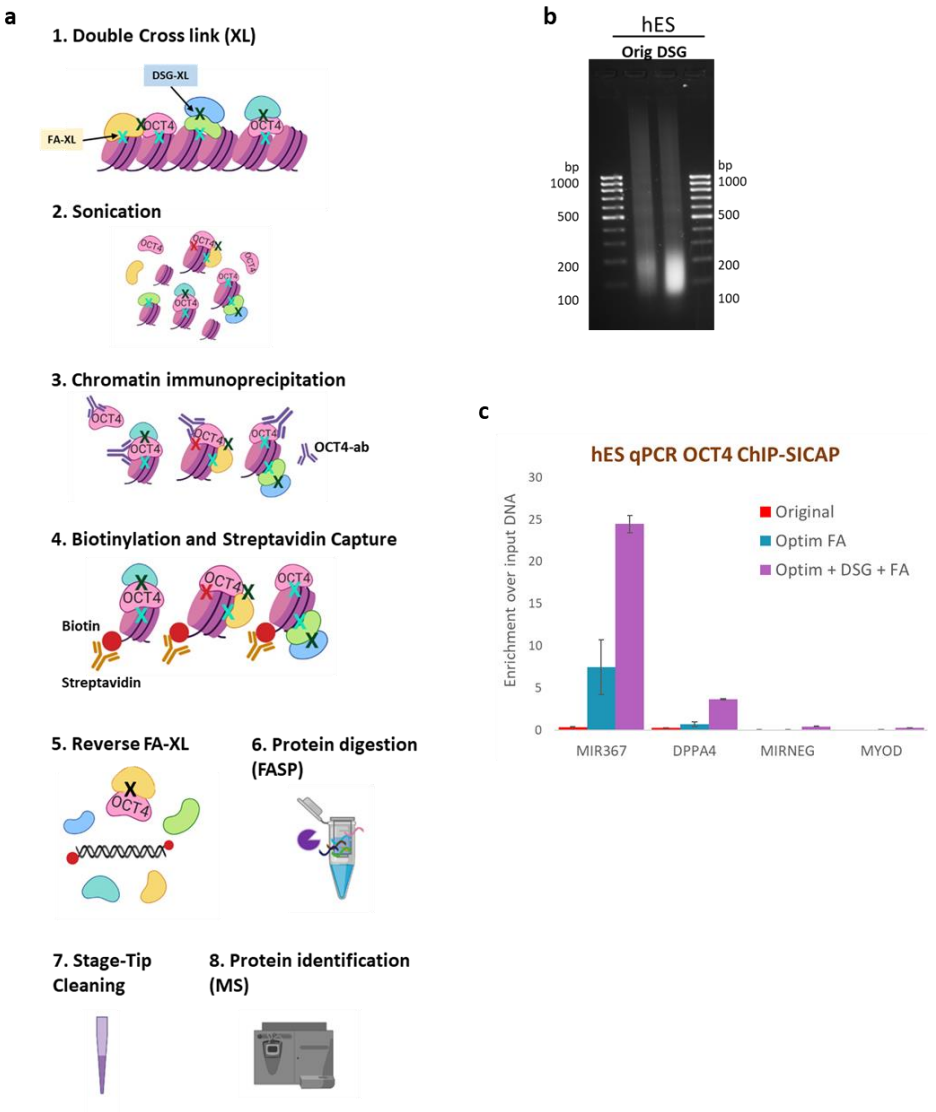


Fig. 3.3 Modifications of ChIP-SICAP protocol using hES. a. Workflow of the adapted ChIP-SICAP method, including the addition of DSG Crosslink (XL) and the protein digestion using FASP. b. Comparison of chromatin sonication of hES cells at 90m using the reported protocol for ChIP-SICAP against the modified protocol using DSG. c. Comparison of the qPCR enrichment analysis in hES for two positive (MIR367 and DPPA4) and two negative (MIRNEG and MYOD) genome regions that are known targets of OCT4 using the DNA obtained from the Original ChIP-SICAP protocol (Original, red), the modified protocol with only Formaldehyde (FA) cross-link (Optim FA, blue) and the modified protocol with DSG and FA cross-link (Optim + DSG + FA). ChIP-SICAP protocol image was created with BioRender.com.

3.3.2 ChIP-SICAP successfully mapped the chromatin-associated OCT4 interactome in human embryonic stem cells

The modified ChIP-SICAP protocol was then applied to hES with OCT4 as the bait, using IgG as a negative control. Two replicates were analysed for each condition (Fig.3.4a). The enriched proteins were digested using the filter aided sample preparation method (FASP) followed by concentration and cleaning of the peptides with stop-and-go –extraction tips (StageTips) (Fig. 3.3a). Both, FASP and StageTips are widely used in of proteomic workflows, as they are highly efficient and convenient for processing, concentrating and cleaning complex protein mixtures prior to mass spectrometry [223, 224]. Briefly, FASP enables protein digestion and peptide purification with the aids of a standard ultrafiltration device adapted with a molecular weight cut-off (MWCO) membrane, where protein mixtures can be chemically modified and digested, while removing detergents and excess reagents. StageTips uses chromatographic beads immobilized in a Teflon meshwork (membrane) to retain and concentrate the digested peptides for further washes without losing material while allowing their elution with high efficiency. This combination of methods were selected as they have been reported to provide a high yield enrichment streamlined protocol for rapid and sensitive proteome mapping, applicable to small amounts of sample [224]. Digested and cleaned peptides were processed by liquid chromatography-mass spectrometry (LC-MS). MaxQuant software was used to process the data using the Andromeda search engine for feature extraction, peptide identification, and protein inference against the UniProt human database. In addition, a label-free quantification analysis was performed using MaxLFQ, an algorithm that defines the abundance of each protein based on the peptides intensities and without the need of a metabolic or chemical labelling [190]. Total numbers of identified proteins for each replicate are summarized in Fig. 3.4b. For both OCT4 hES replicates the number of identified proteins was significantly higher when compared with the IgG controls, suggesting low background protein contaminants. After both OCT4 hES were filtered against the controls (>1.5 fold, FDR <0.1), a total number of 308 proteins present in both replicates were identified as OCT4 chromatin-associated proteins in pluripotency maintenance (Fig. 3.4d). OCT4 was identified amongst the top hit proteins in both OCT4 hESCs replicates (Fig. 3.4c), while not identified in either control, indicating a successful and specific immunoprecipitation of OCT4 in hESCs. Gene Ontology analysis of each

condition revealed the enrichment of nuclear proteins, as well as proteins involved in chromatin structure and transcription regulation, proving that the ChIP-SICAP protocol was successful in pulling-down and isolating OCT4 and chromatin-associated proteins (Fig. 3.4e-g) (Appendix Table 1).

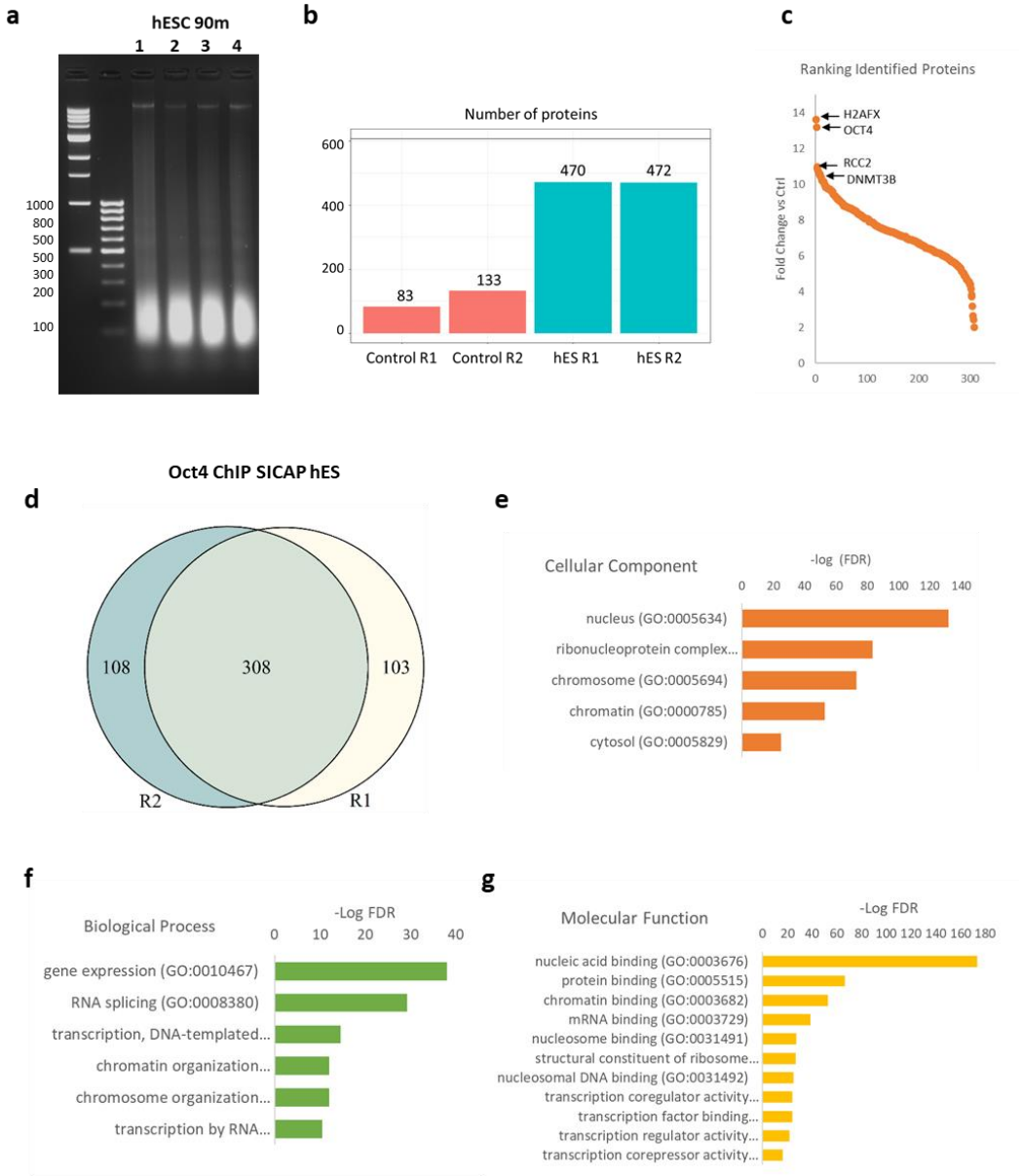


Fig. 3.4 OCT4 ChIP-SICAP protein identification in hES. a. Chromatin sonication of the hES samples used for ChIP-SICAP. b. Total number of identified proteins in each replicate for hES using OCT4 as a bait and hES Control using IgG as bait. c. Identified proteins ranked by enrichment over control. d. Venn diagram of the intersection between both hES OCT4 replicates and statistically significant against the control. e, f and g. Gene Ontology enrichment analysis for Cellular component (e), Biological Process (f) and Molecular function (g) of the identified proteins.

3.3.3 OCT4 shares important pluripotency maintenance partners in mouse and human embryonic stem cells

When first described, ChIP-SICAP protocol was implemented for the expansion of the pluripotency maintenance network in mESC by analysing the chromatin-associated proteins of the pluripotency factors OCT4, SOX2 and NANOG (OSN). In total, 407 proteins were shared between OSN as part of a core pluripotency maintenance network in mouse. Particularly for OCT4, 550 proteins were identified [179].

The OCT4 interacting proteins identified human ESCs were compared to those identified in mouse ESCs to first address the performance of the modified ChIP-SICAP in human, and secondly to describe if despite being different species and with different pluripotent state, similarities and differences exist between human and mouse OCT4 interactomes. A total of 193 proteins were shared between both OCT4 interactomes (Fig. 3.5). Gene Ontology of common interactors revealed their involvement in chromatin remodelling, gene transcription and mRNA splicing processes. The main proteins involved in the transcriptional regulation of pluripotent stem cells were part of the shared proteins, including OCT4, SOX2, STAT3, LIN28A, DPPA4, DNMT3A, SALL4 and L1TD1 [151, 225-227]. Complex enrichment classified most of the proteins into complexes that have been described to be important for chromatin structure and pluripotency maintenance, such as NURD/MBD3, SWI/SNF, LARC, SNWI and the Large Drosha Complex [228-230](Fig. 3.5). Similar biological processes, such as chromatin structure, transcription regulation and splicing were enriched in both human and mouse unique OCT4 chromatin-associated interactors. Interestingly, some of the non-shared proteins could be grouped in the same family or protein type group zinc finger proteins (ZNF) and RNA binding motif (RBM) (Fig. 3.5). This evidence suggests that despite not belonging to the same family, functionally-orthologous proteins are interacting with OCT4 to maintain pluripotency in both species. These differences could also be reflecting the different signalling and routes that govern pluripotency maintenance in each species that converge in the interaction with OCT4. It may also highlight the difference of the pluripotency state adapted by human and mouse ESCs, as hES are more related to EpiSCs and the primed state of pluripotency, in contrast with the naïve state of mESCs.

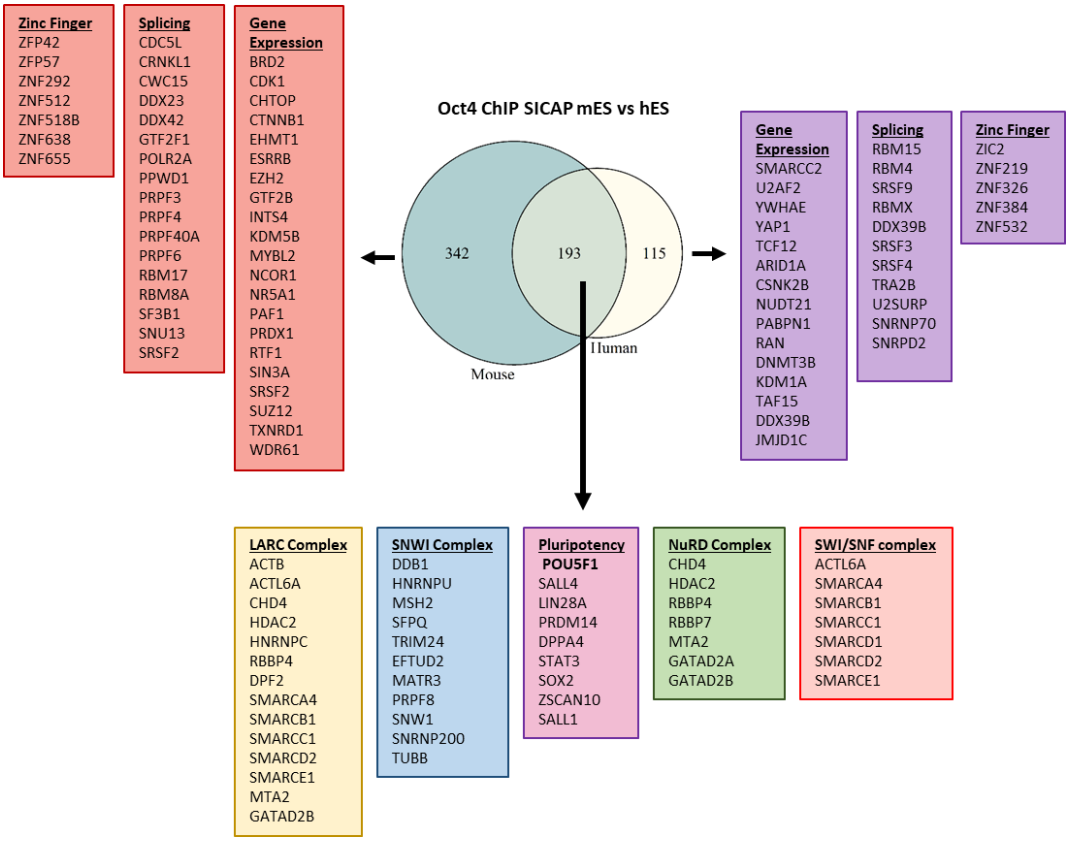


Fig. 3.5 mESC vs hES OCT4 ChIP-SICAP. Venn diagram of the overlapping and unique interactors identified in human and mouse ES cells. Boxes represent groups of proteins for each group: shared proteins in both species and unique for each species.

Overall, the comparison of the OCT4 interactome between human and mouse confirms that conserved pathways and proteins are necessary for the regulation and maintenance of pluripotency and stem cell self-renewal. Moreover, it allowed the identification of unique interactors for each species, illustrating the different pathways that govern and differentiate human and mouse pluripotency maintenance. Finally, the overlap of important pluripotency maintenance factors in human and mouse using the original method increased the confidence in the results obtained with the adapted protocol of ChIP-SICAP in human cells.

3.3.4 OCT4 establishes an expansive protein network with the somatic chromatin during early stages of reprogramming

Having identified the OCT4 chromatin-associated proteins in pluripotency, the adapted protocol was applied to define the OCT4 protein interactors in early reprogramming. The

time point defined as early reprogramming stage was established following the criteria used to investigate the initial engagement of OSKM with the somatic genome. This study established 48 hrs after the induction of the OSKM factors in human fibroblasts as an early point of reprogramming as they observed it was the earliest for maximal OSKM expression, it preceded major transcriptional changes and it preceded the time when the fibroblasts are changed to ES growth conditions in their reprogramming protocol [110]. Using a doxycycline (dox)-inducible lentivirus transduction system, the OSKM factors were transcriptionally induced in human fibroblasts [231] (Fig. 3.6a). After 48 hours post dox inductions, changes in cell morphology were already observed when compared with HF with no OSKM (Fig. 3.6b). Western blot confirmed the presence of OSKM, with no detection in HF controls (Fig. 3.6c). Immunocytochemistry (IC) assays demonstrated the expression of the four OSKM factors (Fig. 3.6d), indicating high efficiency lentivirus transduction suitable for studying OCT4 in early reprogramming (OSKM 48h).

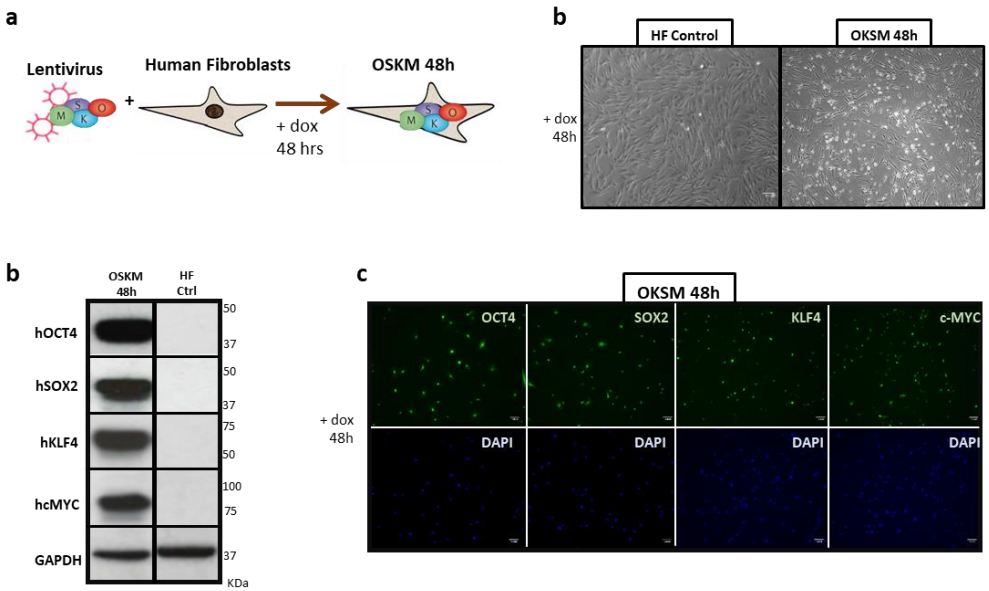


Fig. 3.6 Induction of exogenous OSKM factors in HF. a. Workflow of OSKM induction showing the transduction of Human Fibroblasts with the lentiviruses, followed by the addition of dox and the induction of OSKM expression for 48h. b. Images of non-transduced Human Fibroblasts (HF Control) and OSKM induced cells after 48 hours of dox addition. c. Western Blot analysis of each OSKM factor after 48 hours of cell induction. HF were used as a negative control showing no expression of OSKM. d. Immunocytochemistry of each OSKM factor after 48hrs of cell induction. DAPI staining is shown to visualize the cells.

After OSKM induction and cross-linking, optimal sonication time was established at 140 min (Fig 3.7a). ChIP-SICAP as described above was carried out in two replicates, using HF with no OSKM induction as negative control. Mass spectrometry analysis identified the LFQ intensities of each enriched protein.

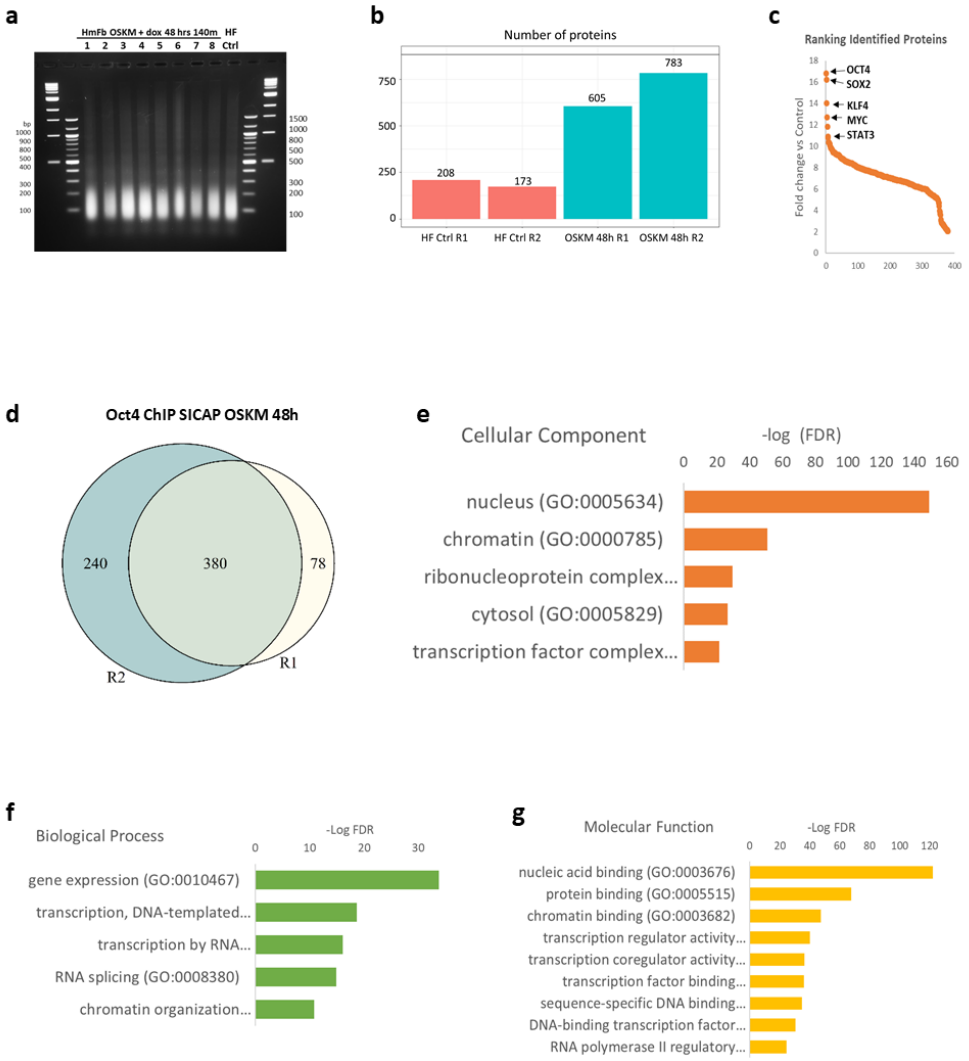


Fig. 3.7 OCT4 ChIP-SICAP protein identification in OSKM 48h. a. Chromatin sonication of the OSKM 48 and HF control samples used for ChIP-SICAP. b. Total number of identified proteins in each replicate of HF control and OSKM 48h using OCT4 as the bait. c. Identified proteins ranked by enrichment over control d. Venn diagram of the intersection between both OSKM 48h OCT4 replicates and statistically significant against the control. e, f and g. Gene Ontology enrichment analysis for Cellular component (d), Biological Process (e) and Molecular function (f) of the identified proteins.

Total numbers of proteins identified for each replicate are summarized in Fig 3.7b. As observed in hES, more proteins were identified in the OSKM 48 replicates than in the control. After filtering out proteins identified in the control sample (>1.5 fold, FDR<0.1), 380 proteins were identified as OCT4 chromatin associated proteins in OSKM 48h (Fig. 3.7d) (Appendix Table 1). OCT4 was again one of the most enriched proteins and was not identified in either control (Fig. 3.7c). GO analysis revealed the enrichment of nuclear proteins, as well as proteins involved in chromatin structure and transcription (3.7e-g). This ChIP-SICAP analysis therefore reveals that OCT4 engages the somatic chromatin during the early stages of reprogramming by mainly involving gene regulation and chromatin organization proteins.

3.3.5 The OCT4 chromatin-associated interactome during pluripotency is distinct from that in hESCs.

To further investigate the main differences and similarities between the OCT4 chromatin-associated proteins during pluripotency maintenance and early reprogramming, both interactomes were compared. As both set of samples were run using the same MS workflow, it was possible to normalize the label-free quantification values (LFQ) acquired for each protein in each condition and perform differential enrichment analysis. Principle component analysis (PCA) of OSKM 48h, hES and their respective controls clustered the OCT4 interactors of OSKM 48h in a different group from those in hES (Figure 3.8a), suggesting significant difference between both conditions. To further describe the similarities and differences, the 308 and 380 OCT4 interactors defined previously for each interactome (filtered against their respective controls >1.5 fold enrichment) were compared. First, the overlap analysis between both OCT4 interactomes revealed 149 sharing proteins between hES and OSKM 48h, and 231 and 160 unique interactors for OSKM 48h and hES respectively (Fig. 3.8b).

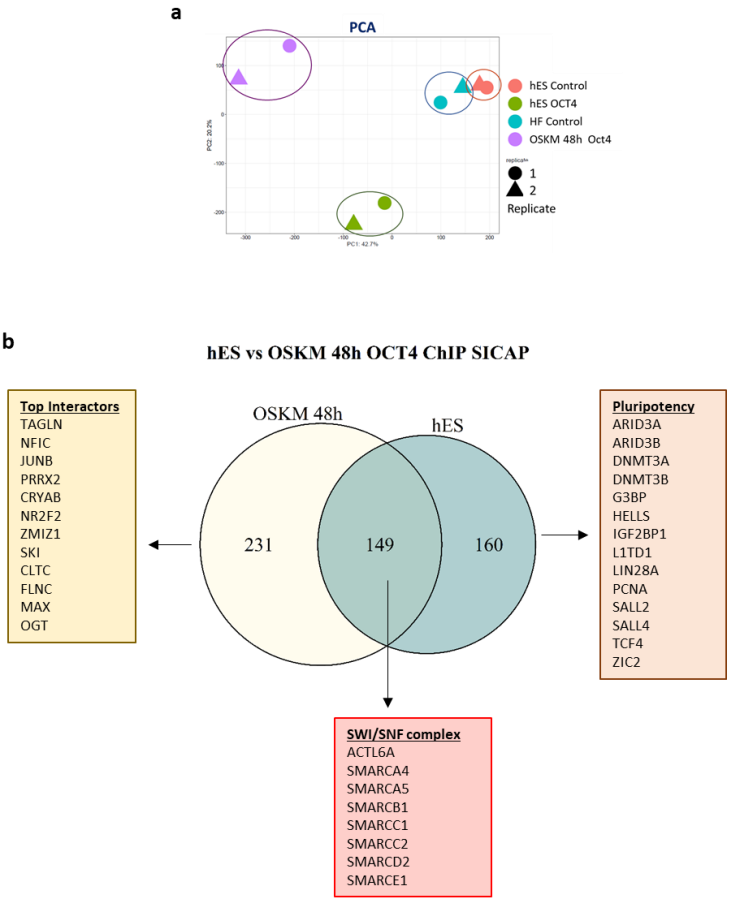


Fig. 3.8 Comparison of OCT4 ChIP-SICAP in pluripotency and reprogramming. a. PCA score plot of total ChIP-SICP dataset obtained for hES and OSKM 48h including their respective controls. b. Venn diagram of the common and unique proteins identified in the OCT4 ChIP-SICAP of hES and OSKM 48h. Boxes indicate examples of shared and unique proteins for each interactome.

Further quantitative analysis between both set of OCT4 interactors was applied to describe the differential enrichment of the shared and unique proteins. The analysis was performed using the Perseus software, which considers the LFQ values of each protein (non-labelled quantitative proteomics) and using a t-test with FDR < 0.1 and difference > 1.5 log(fold) as the cut-off values. A total number of 78 proteins were significantly enriched in hES when compared to OSKM 48h, 243 significantly enriched in OSKM 48h when compared to hES and 226 showed no significant difference between both conditions (Supplementary table 2) (Fig. 3.9). These differences and similarities between the OCT4 interactomes in hES and OSKM 48h are visualised using a volcano plot (Fig. 3.9a). Network analysis using STRING and Cytoscape show the connections between the identified proteins (edges) as reported in the literature as well as the colour-coded

intensity of enrichment (Fig. 3.9b). Colour coding was based in the fold changes obtained in the enrichment analysis, where green represents enriched proteins in hES and red proteins enriched in OSKM 48h and black no change between both interactomes (Fig. 3.9b).

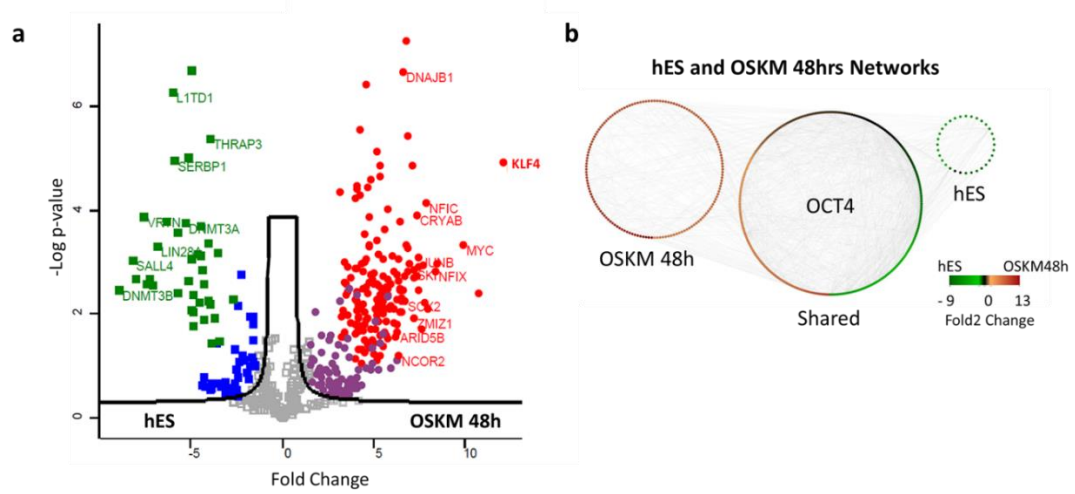


Fig. 3.9 Quantitative differential analysis between pluripotency and early reprogramming OCT4 ChIP-SICAP. a. Volcano plot of differentially abundant OCT4 interacting proteins between hES and OSKM 48h Red dots denote enriched and unique proteins in OSKM 48h, purple dots denote enriched proteins in OSKM 48h that are also present in hES, green squares denote enriched and unique proteins in hES, blue squares denote enriches proteins in hES that are also present in OSKM. b. Network comparison between the OCT4 chromatin-associated proteins identified in hES and OSKM 48h. Network was constructed using the String plug-in in Cytoscape. Edges represent interactions reported in the literature. Colour coding represents the level in abundance of each protein (fold change).

Most enriched proteins included the unique interactors for each condition (green for hES and red for OSKM 48 in the volcano plot Fig. 3.9a and network 3.9b).OCT4 interactors that are uniquely enriched in hESCs included proteins known to be important for pluripotency maintenance (LIN28A, DNMT3A, L1TD1, SALL4, SALL2, DNMT3B) [151, 225-227]. On the other hand, OCT4-interactors mostly enriched in early reprogramming included proteins previously described to have roles in reprogramming, such as OGT [168], RUNX1 [154] and MBNL1 [232], but also included new interactors with no previous association with reprogramming, such as TAGLN, CRYAB, GBE1, PRRX2 and MAFF. Interestingly, there was a group of proteins that were associated with OCT4 in both pluripotency maintenance and early reprogramming (blue in hES and purple in OSKM 48h in the volcano plot (Fig. 3.9a) and black in the network (Fig 3.9b)) but were more enriched

in one condition over the other one. For example, the nuclear export factor XPO1, which has been associated in the nuclear transport of OCT6 [233], was identified in both early reprogramming and pluripotency but with higher levels in the OSKM 48h interactome. On the contrary, topoisomerase II alpha (TOP2A), a highly expressed protein in undifferentiated cells was also shared in OSKM 48h and hES interactomes, but with higher levels in hES [234]. It is worth mentioning that OCT4 was also included in the category of shared proteins with different abundance reflecting the high protein level of ectopic OCT4 in OSKM 48hr compared to the endogenous OCT4 levels in hESCs. This differential expression could be influencing how OCT4 interacts to other chromatin-associated proteins as well as their enrichment. However, it was interesting to identify shared proteins with no difference in abundance between hES and OSKM 48h, suggesting that despite higher quantities of OCT4, not all the interactors in OSKM 48h were also increasing. For example, proteins involved in the SWI/SNF complex (SMARCA4, SMARCA5, ACTL6A, SMARCB1, SMARCC1, SMARCC2, SMARCD2, SMARCE1) (Fig. 3.9a (grey dots)) were detected in both interactomes with the same abundances. This chromatin-remodelling complex has important roles in both pluripotency maintenance and reprogramming [235]. The similar protein enrichment of these complexes may indicate that similar amount of interactions of this complex with OCT4 are required for reprogramming and pluripotency maintenance, despite the different protein levels of OCT4.

Overall, comparison of the OCT4 chromatin-associated proteins in pluripotency and early reprogramming reflected the functional adaptation of OCT4 and its interactions to either maintain pluripotency or induce pluripotency in differentiated cells. Nevertheless, the shared proteins identified in both processes suggests common functions of OCT4 are also required for reprogramming and pluripotency maintenance. And most importantly, the new set of unique interactors identified in early reprogramming revealed for the first time the differential OCT4 engagement with chromatin proteins in early reprogramming when compared with its OCT4 engagement in pluripotency and proposes for the first time the gain of new and specific interactors for the reprogramming process.

3.3.6 OCT4 engagement with the somatic genome differs during pluripotency maintenance and reprogramming

Previous reports of the initial engagement of OSKM in early reprogramming with the somatic genome when compared to pluripotency maintenance established differential binding patterns [110]. As these studies were performed in protocols that only cross-linked with FA, ChIP-seq on OCT4 was performed for OSKM 48h and hESCs implementing the double cross-link DSG+FA steps, with the aim of investigating if the addition of DSG had any effect in the OCT4 DNA engagement profile. To define DNA enrichment of OCT4 in ChIP-seq, double cross-linking, sonication and chromatin immunoprecipitation were carried out in a new set of samples (hES and OSKM 48hr) following the same cell culture and ChIP conditions applied to the set used for protein identification, but focused in the purification of DNA for sequencing instead of the protein fraction. (Section 2.2.12 Materials and Methods). The DNA from three ChIPs for each condition were sequenced and aligned to the human genome. A model-based analysis for ChIP-seq (MACS)[207] was used to identify genomic regions enriched for unique-mapped reads from ChIP-DNA over the input DNA identifying 89,262 and 169,071 enriched peaks for hESCs and OSKM 48h respectively (Fig. 3.10a). To further investigate the similarities and differences between the binding patterns of OCT4 in hESCs and OSKM 48h, peaks were grouped in shared and unique among the samples and peaks intensity was measured and visualized in a read density heatmap (Fig. 3.10a). For both, unique and shared sites, the intensity of the peaks revealed a high binding affinity. Most interestingly, only 8,100 binding sites were shared between hESCs and OSKM48h, corresponding to only 10% and 5% of the total binding sites for hESCs and OSKM respectively (Fig. 3.10a). Moreover, OCT4 did not target NANOG at early reprogramming, which is activated and targeted in late stages and in pluripotency, as observed by the its targeting in hESCs, therefore, corroborating the peak calling results obtained. (Fig. 3.10b). Additionally, the peaks visualization showed that double cross-link with DSG+FA did not affect the quality or quantity of the data, nor resulted in an increase of unspecific bindings and background signal (Fig. 3.10b). Overall, the low peaks overlap detected between hESCs and OKSM 48h agrees with previous work reporting different engagement of the OSKM factors at early reprogramming when compared with pluripotency maintenance and correlates with the ChIP-SICAP findings of different chromatin-associated proteins interactions of OCT4 in both conditions.

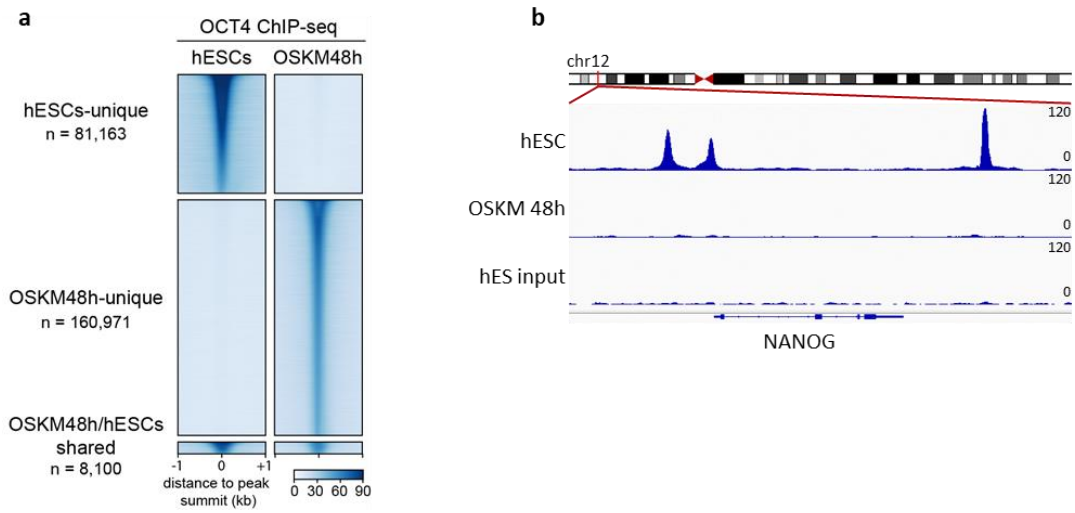


Fig. 3.10 Different engagement of OCT4 with somatic genome at early reprogramming and during pluripotency maintenance. a. Read density heatmaps (in blue scale) showing the intensity of hES OCT4 and OSKM 48h ChIP-seq peaks spanning ±1 kb from the centre of the peak summit of the unique and shared peaks for hES an OSKM 48h. The number of targeted sites is indicated for each condition. b. hES, OSKM 48h and Input OCT4 ChIP-seq profiles at Nanog locus. Peak presented are normalized against input DNA sequenced tags.

3.3.7 The distinct OCT4 interactomes are not driven by pre-existing protein levels

Pluripotent stem cells and human fibroblasts are different cell types with particular transcriptional and proteomic profiles as they both require cell-type specific gene expression to maintain their cell identity. To identify the extent by which the pre-existing protein abundance influence the OCT4 interactome in each cell, quantitative proteomic profiles were determined in human fibroblasts and ESCs using stable Isotope Labelling with amino acids in cell culture (SILAC).

SILAC is a metabolic quantitative proteomic method that depends on cellular protein synthesis to incorporate specific stable isotope-containing amino acids in each sample to be compared. Cells of interest are grown in parallel but in two different medium formulations: the light and the heavy. Light medium contains the amino acid with the natural isotope, while the heavy contains the stable isotope-containing amino acid. Once cells adapt to the media and reach an amino acid incorporation of ≈97% (after 5 cell divisions), cells can be processed for whole protein extraction with standard protocols and mixed in similar ratios for mass spectrometry analysis. Because the difference in mass of the labelled amino acids is known, the identified peptides can be distinguished

and assigned to the sample of origin. Then, the signal intensities between the light and heavy peptides are used to give the relative protein abundance between both conditions (Fig. 3.11a) [236].

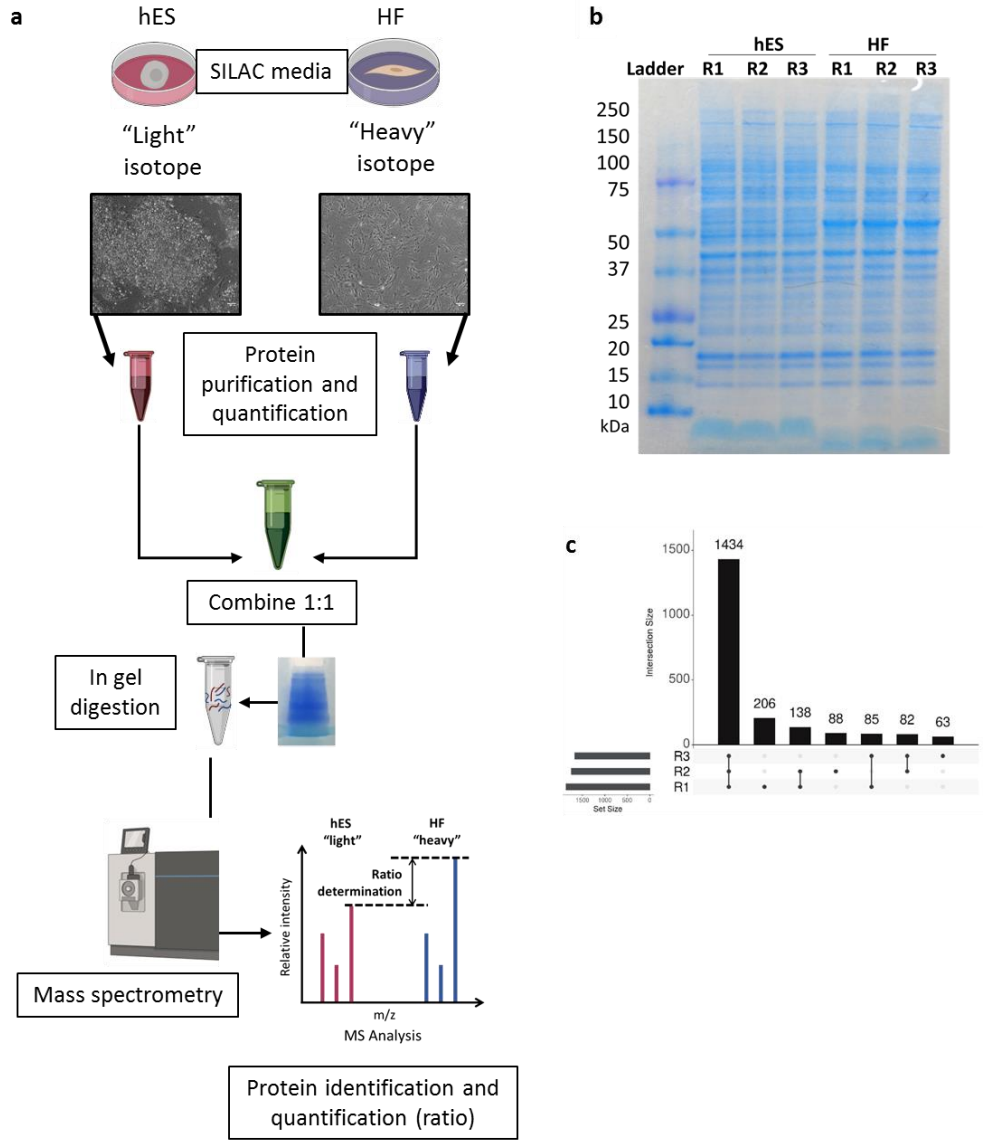


Fig. 3.11 SILAC-based quantitative proteomics of hES and HF proteomes. a. Workflow of the SILAC protocol followed for the quantification analysis. a. Representative images of hES and HF grown in SILAC media and of SDS-PAGE gel used for in-gel digestion are shown. b. SDS-PAGE analysis of the total protein extracts of hES and HF grown in SILAC media. Three replicates were analysed. Gels were loaded with 10µg for each sample and visualized by Coomassie Blue. c. Upset plot showing the shared and unique proteins identified in the three SILAC replicates analysed.

After hESCs and HF were grown in SILAC medium for at least five passages, proteins were collected from whole cell lysates in three biological replicates (Fig. 3.11). SDS-PAGE

reveal clear differences in the protein banding patterns between HF and hES, confirming the different protein content in each cell type (Fig. 3.11b). Same amounts of protein of each condition were mixed and processed using in-gel digestion and Stage-Tip cleaning procedures before protein identification and quantification by mass spectroscopy. MaxQuant software and the plugin for SILAC quantitative proteomics were used to determine the protein levels ratios between both samples (HF/hES) (Appendix Table 2) [193].

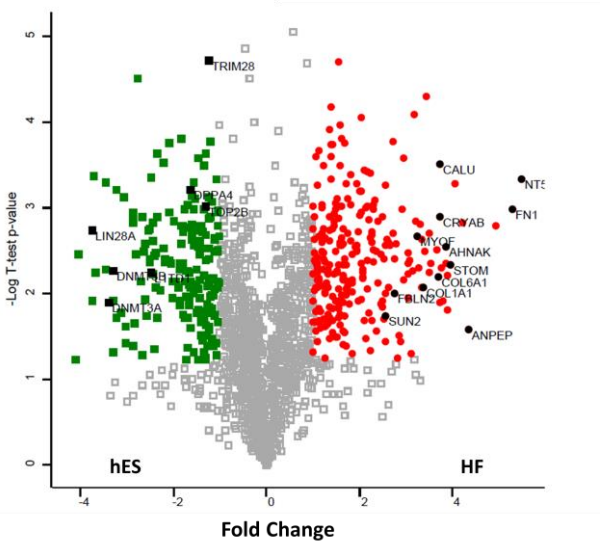


Fig. 3.12 Quantitative analysis of hES and HF proteomes with SILAC. Volcano plot of differentially expressed proteins between hES and HF. Red dots denote higher levels of proteins in HF, green squares denote overexpressed proteins in hES.

The identified and quantified proteins showed high overlap between the three replicates Fig. 3.11c. Differential expression analysis (log fold>1, FDR<0.1) revealed the highly expressed proteins in hES (green in volcano plot Fig. 3.12), which were known to be associated with pluripotency maintenance such as LIN28A, DNMT3A, DNMT3B, EPCAM and L1TD1 [151, 225-227]; as well as proteins highly expressed in HF (red in volcano plot Fig. 3.12), which included proteins associated with epithelial cells and fibroblast markers, such as NT5E [237], CRIP2 [238], CRYAB [239] and VIM[240]. These results support that SILAC analysis has successfully identified the different protein profiles present in human ESCs and fibroblasts.

Next, SILAC data was used to investigate the protein levels of only those that interact with OCT4 in h hES and OSKM 48h. For this analysis, the OCT4 interactors in hES and OSKM 48h were classified into three groups: interactors over-represented in hES vs OSKM (Fig. 3.13a), interactors over-represented in OSKM 48h vs hES (Fig. 3.13b) and interactors with similar enrichment in hES and OSKM 48h (Fig. 3.13c). Protein level profiles were visualized using heatmaps, where protein abundance is reported as the ratio HF/hES, meaning higher values represent overexpressed proteins in HF vs hES (red) and lower values represent overexpressed proteins in hES vs HF (green)(Fig. 3.13).

The enrichment of most differential OCT4 interactors did not correlate with the measured protein levels in the corresponding cell type. Only a small set of enriched interactors in hES interactome reflected the high protein levels in hESCs including the pluripotency maintenance proteins DNMT3A, DNMT3B, and LIN28A [145, 241](Fig. 3.13a). The same was observed for a small set of OCT4 interactors enriched in OSKM 48h that also showed high protein levels in HF including the somatic proteins LGALS1, CRIP2, CRYAB [238, 239, 242] (Fig. 3.13b). These particular examples illustrate that for some proteins there was in fact a correlation between the enriched interaction and higher protein levels, but it was not the case for the vast majority of proteins that differentially interact with OCT4. In each group analysed, most interactors had the same expression levels in hES and HF (black in the heatmaps (Fig. 3.13), even if they were defined as enriched OCT4 interactors in either pluripotency or early reprogramming. For example, ANXA5, PRPF4, RTCB, IPO7, IPO5 and TPM3 were enriched interactors in OSKM 48h vs hES but had similar protein levels in both HF and hES. Moreover, differentially OCT4 interactors were sometime less abundant in the cell type were the interaction is more enriched. For example, STAT3, XPO1, CDK1, XPOT and KPNA2 showed more enriched interaction with OCT4 in OSKM 48h over hESCs despite being more abundant in hES than HF. Furthermore, proteins which interacted with OCT4 at similar enrichment in hES and OSKM 48h regardless of their differential levels in both cell types. For example, H1FX, PPP1CA and SFRS4 had higher protein levels in HF, while FASN, RAN, PRDX6 and PEBP1 had higher levels in hES, but all of them were interacting at similar levels with OCT4 in hES and OSKM 48h. In summary, the SILAC analysis revealed that the pre-existing protein

levels in hESCs and HF is not the sole determinant that drives the differential OCT4 interactomes observed during pluripotency maintenance and early reprogramming.

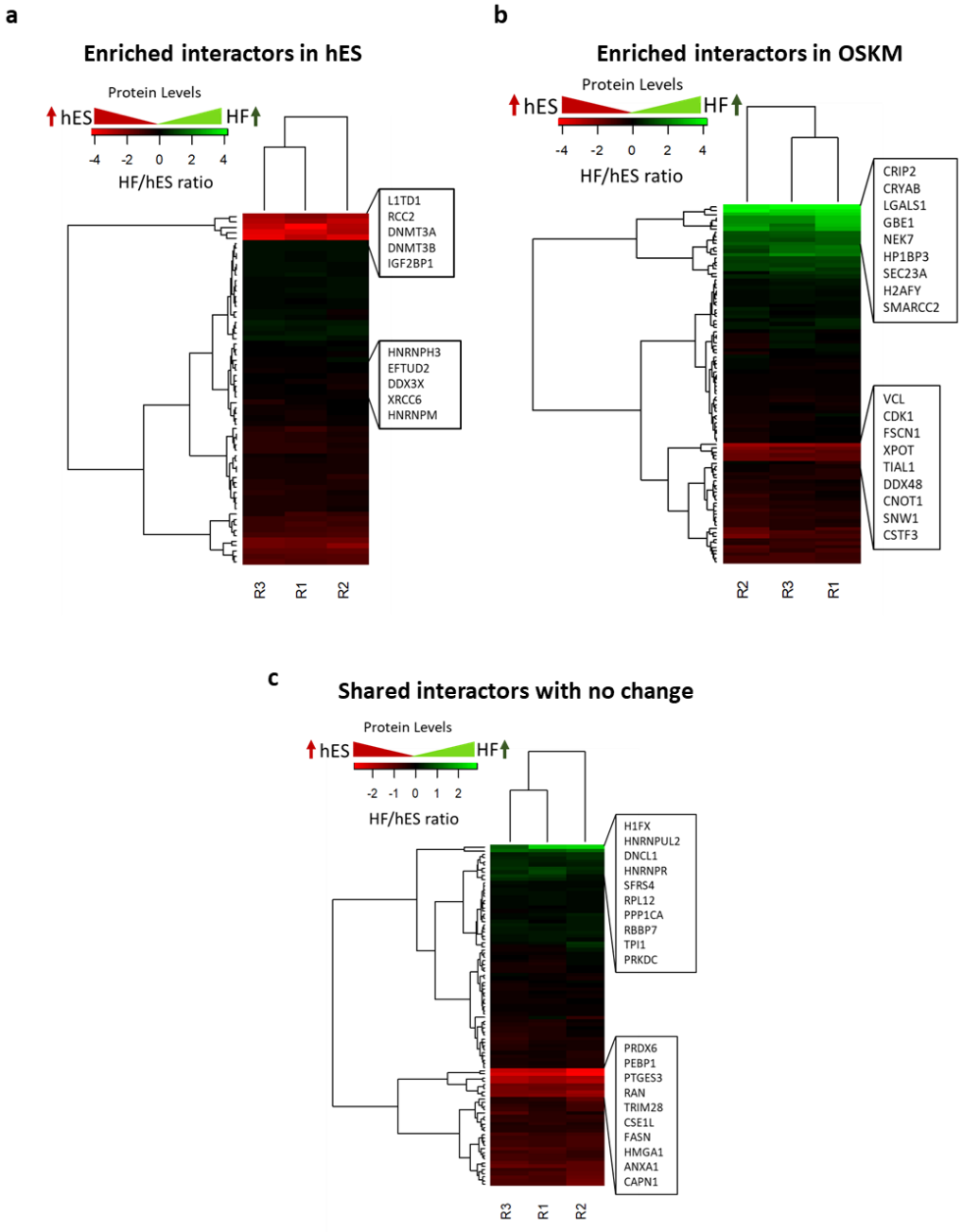


Fig. 3.13 Protein levels of OCT4 interactors in hES and HF. Protein levels of OCT4 interactors relative to their expression in hES and HF. Proteins were clustered according to the HF/hES ratio and displayed as a heatmap. Green represents high expression in hES, red represents high expression in HF and black represents similar expression. a. Enriched OCT4 interactors in hES. b. Enriched OCT4 interactors in OSKM 48h. c. OCT4 interactors with no difference between hES and OSKM 48h.

Similar results were observed when transcriptomic profiles of the OCT4 interactors were determined using published microarray expression data sets of HF, iPS and ES cells [95, 110, 243]. The analysis was carried on using the same three groups: interactors with enrichment in hES vs OSKM (Fig. 3.14a), interactors with enrichment in OSKM 48h vs hES (Fig. 3.14b) and shared interactors with no significant change between hES and OSKM 48h (Fig. 3.14c). To analyse the transcriptomic profiles of each group, instead of ratios as in SILAC, gene expression levels were used for each protein in each cell type, followed by the hierarchical clustering and visualization in heatmaps. As observed with the protein levels, the gene expression was not the main influence of the interactions of OCT4 in each condition (hES or OSKM 48h), as for each group there were set of genes with similar expression levels, higher expression levels and lower expression levels (Fig. 3.14 black, red and green respectively) that did not correlate with their enrichment levels reported in the OCT4 interactomes in either pluripotency or reprogramming. Both the proteomic and transcriptomic profile analysis revealed that OCT4 interactions are not exclusively determined by the gene expression or protein levels of the interactors in each cell type.

Altogether, the results in this chapter describe for the first time the OCT4 chromatin associated proteins in human pluripotency and early stages of human reprogramming to iPSCs, revealing that OCT4 does not only interacts differently with the somatic genome, but also acquires new protein interactions that could be of high relevance for the reprogramming process.

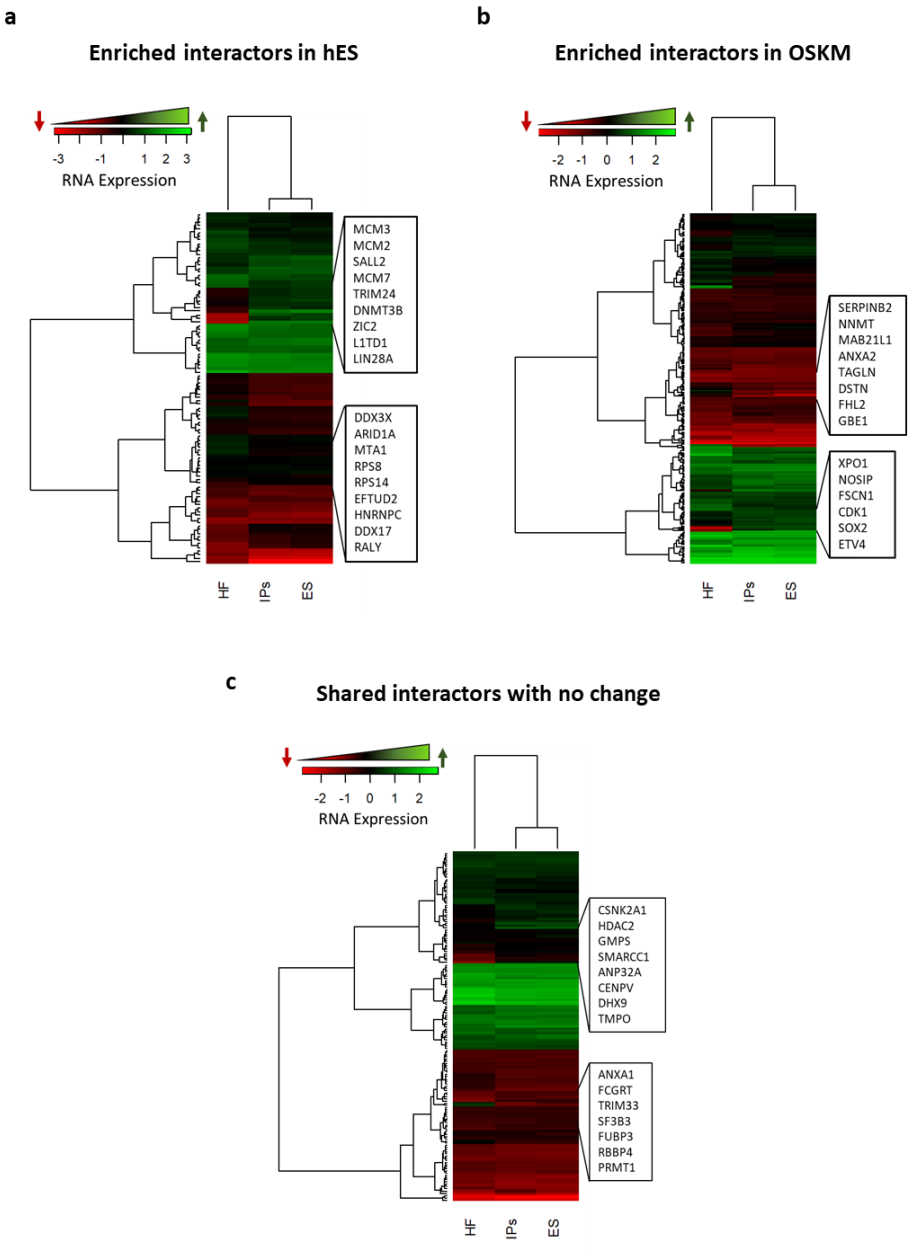


Fig. 3.14 RNA Expression profiles of OCT4 interactors in hES and HF. RNA expression profiles of OCT4 interactors in HF, iPS and hES. Genes were clustered according to their expression in HF, iPS and hES and represented as a heatmap. Green represents high expression, red represents low expression. a. Enriched OCT4 interactors in hES. b. Enriched OCT4 interactors in OSKM 48h. c. OCT4 interactors with no difference between hES and OSKM 48h. Raw data obtained from [110]

3.4 Discussion

OCT4 is critical to maintain the pluripotency of embryonic stem cells (ES) and to induce pluripotency in the reprogramming process to induced pluripotent stem cells (iPSCs). Multiple biochemical approaches, using mostly mouse as the model of study, have focused in deciphering the molecular basis for pluripotency defining OCT4 as a key component of the core regulatory network that governs ES pluripotency, along with SOX2 and NANOG [69, 82, 84, 225, 244]. Most of these studies have reported that OCT4 is involved with multiple chromatin remodelling and epigenetic regulatory protein such as polycomb group proteins [79], SWI/SNF proteins [235] and Mi-2/NuRD complex proteins [245]. Expansion of mouse OCT4 interactomes has also help to dissect important biochemical basis for OCT4 diverse roles in both genetic and epigenetic regulation of mouse stem cell pluripotency that could be translated to the reprogramming process [82, 87, 172, 173]. However, since the first isolation of embryonic stem cells and the iPSCs, one of the major challenges of developmental and reprogramming cell biology has been trying to understand and dissect specific contributions of OCT4 to each process. Particularly in human cells, limited information is available regarding the general OCT4-associated protein complexes in both pluripotency and reprogramming and how they dictate the different OCT4 critical regulatory activities. To overcome this lack of knowledge, adaptation of one of the most recent protocols developed that combines ChIP and MS called Selective isolation of chromatin-associated proteins via ChIP (ChIP-SICAP)[179] (Fig. 3.1), was successfully applied in this work allowing the identification of OCT4 and its chromatin partners during human pluripotency maintenance and early reprogramming.

ChIP SICAP was first described as a protocol to expand the pluripotency network of mouse ES cells, focusing particularly in chromatin-associated proteins, allowing both a clean and reproducible technique to identify the chromatin-associated proteins of the pluripotency factors OCT4, SOX2 and NANOG, as well as DNA purification for next generation sequencing and identification of the genomic binding regions of the latter [179]. Modifications to the original protocol needed to be implemented when tested in this thesis for human ES as the first attempts resulted in a poor protein recovery (Fig. 3.2). One of the main modifications was the extra cross-linking step via DSG (Fig. 3.2).

This additional step was fundamental for the stabilization of protein-protein interactions, which, in combination with the standard formaldehyde, allowed a better capture of protein-DNA by increasing the OCT4 DNA-binding signal-to-noise ratio in the ChIP and the number of identified proteins when analysed by Mass Spectrometry (Fig. 3.3). It is noteworthy that, this chapter focused on protein identification, next generation sequencing of DNA will be discussed in the chapter 5. Overall, the modified protocol allowed the purification of OCT4 chromatin associated proteins involved in transcription regulation, chromatin structure and mRNA splicing (Fig. 3.4). In addition, it proved to be consistent in the two different human cell conditions: pluripotency maintenance and early reprogramming.

A discussion of the relevance of these findings is addressed next.

3.4.1 Main pluripotency maintenance factors are shared between mouse and human OCT4 interactomes

A key unanswered question in developmental cell biology is how much of the knowledge available for OCT4 in mouse ES can be translated to human pluripotency. Although the main objective of this work was not to address this question directly, the protocol adaptation performed herein allowed the first identification of the OCT4 chromatin-associated proteins in human ES. By comparing this information with the data already available of the mouse OCT4 interactome using the original ChIP-SICAP protocol; it was possible to report similarities and differences in the OCT4 pluripotency networks of human and mouse. Not to mention that the comparison also allowed the validation of the performance and quality of the adapted method.

Firstly, the overlap between both interactomes revealed a comprehensive number of OCT4 interactors shared between mouse and human, which included more than 50% of the former with 40% of the latter (Fig. 3.5). Unsurprisingly, among these proteins were components of pluripotency maintenance and transcriptional regulators previously reported to be important in both human and mouse, including SOX2, STAT3, LIN28a, SALL4, DNMT3A, DPPA4 and DNMT3B, as well as members of the chromatin remodelling complexes LARC, NURD and SWI/SNF were identified (Fig. 3.5). It has been previously reported that along with the transcription factors, these and many other chromatin

regulators play essential roles in ES and are constantly identified in the different mouse OCT4 interactomes [82, 87, 172, 173, 179]. This evidence confirmed that, in both human and mouse, these proteins are part of a conserved pluripotency network with OCT4 and that the modified of the ChIP-SICAP was a reliable tool.

An interesting complex that has been identified in most of the mouse OCT4 interactomes and that was also detected in the human interactome is the nucleosome Remodelling and Deacetylase complex (NURD) [246]. NURD is unique among chromatin regulators as it integrates the ATP-dependent nucleosome remodelling activity with deacetylase histone activity to create repressive chromatin structure [247]. NURD functions primarily as a co-repressor by altering the nucleosome occupancy to avoid the binding of the transcriptional machinery at the gene promoters [248]. The different combinations of subunits in this complex determine its function and genomic targeting, involving cell-type specific functions and new roles apart from transcription regulation like maintenance of genome stability, DNA replication and DNA repair [247]. In mouse stem cells, different combinations of NURD subunits and associations with other proteins had been described to be important for pluripotency maintenance and differentiation, being NURD/Mbd3 the most important one [249]. Mbd3 subunit is necessary for the recruitment and assembly of the complex and it has been linked to roles in development, as it absence in stem cells leads to defects in differentiation[121]. In addition, a more recent stem cell specific NURD has been reported, which involves the interaction of the specific isoform Mbd3c with Wdr5 [126, 250]. Wdr5 is a histone binding protein that promotes H3K4 trimethylation by binding the histone H3. It has been widely associated with other different chromatin remodelling complexes and with the pluripotency maintenance network, having important roles in self-renewal and induced pluripotency maintenance [126, 250]. Even though the mechanisms involving this stem cell-specific NURD/Mbd3/Wdr5 complex is still unclear, it was interesting to find that all the subunits are also present in the interactome of human OCT4, which could suggest it might also be an important complex in the human context, expanding the relevance and mechanisms in which the NURD complex and Wdr5 are involved in human pluripotency maintenance and stem-cell maintenance.

In addition to the chromatin remodelling complexes, most of the shared and unique proteins of the OCT4 interactome were involved in splicing and miRNA processing. The roles of post-transcriptional regulation and RNA binding proteins had been described to be as important as transcriptional regulation for the pluripotency maintenance network [251]. It is well known that there is an auto regulatory loop between miRNAs and the core pluripotency maintenance network, which leads to repression of developmental genes and a sustained positive feedback of stem-cell specific genes [252]. OCT4 main role in the regulation of miRNAs involves binding their promoters, either activating or repressing their expression [253]. However, findings in this work, could point to an alternative involvement of OCT4 in the regulation of miRNA, mediated by its interaction with the large Drosha complex, which is responsible for miRNAs processing and maturation [254]. The presence of most components of the complex in the human OCT4 interactome here reported, could suggest that OCT4 might be chromatin-associated with this complex as part of a non-previously described regulation of miRNA in stem cells. Additionally, members of the zinc-finger protein family were observed to be shared in both species, as well as some members being unique for each species. Interestingly, zinc finger proteins have been suggested to play an important role in maintenance of ESC pluripotency and differentiation potential as well as proliferation and cell cycle control [255]. For instance, zinc finger protein 206 (Zfp206) is considered a hallmark of pluripotent cells, as it is known to regulate ESC gene expression and differentiation [256, 257]. Rex 1 (also known as Zfp42) is restricted to undifferentiated ESCs contributes to maintain the undifferentiated state, 200, while ZFP57 was shown to maintain the genomic imprints in ESCs [258, 259]. The presence of these and other zinc finger proteins in both mouse and human OCT4 interactomes revealed an important contribution of these family for the maintenance of pluripotency in both species and highlights the fact that for each species distinct members of the same family converge in the interaction of OCT4 and the pathway that governs pluripotency.

The interspecies OCT4 interactome comparison revealed that there is a high conserved OCT4 chromatin-associated pluripotency maintenance network between both species, including complexes and pathways previously reported as fundamental for pluripotency maintenance. Moreover, the more detailed analysis, as exemplified with the NURD and Drosha complex, also suggests that there might be additional chromatin-dependent

shared mechanisms non-previously described in pluripotency where OCT4 is a crucial component. This opens avenues to investigate in more details new pathways involved in both mouse and human pluripotency maintenance as well as to the better understanding of the pathways that differ and contribute to the naïve pluripotency state of mESC and the primed-like state of hESCs, opening the research field to analyse the OCT4 interactome of EpiSCs and investigate if it resembles more the one from hESCs than mESCs, correlating with the more primed state of hESCs.

3.4.2 OCT4 engagement with the somatic proteome in early reprogramming differs from that in pluripotency maintenance

OSKM overexpression in HF for 48hr has already been described as an early reprogramming time point where important transcriptional and proteomic changes take place [110]. Unsurprisingly, when ChIP-SICAP was applied to OSKM 48h, the identification of chromatin-associated proteins revealed that at this early stage OCT4 was already associated with chromatin complexes thorough interacting with proteins (Fig. 3.7). For instance, compared with the pluripotency maintenance interactome, different and new binding partners in OSKM 48h were discovered (Fig. 3.8, 3.9). These differences correlate with the differential OCT4 chromatin-engagement profile between early reprogramming and pluripotency maintenance [110, 260], supporting the idea that OCT4 is involved new processes in the reprogramming context.

To help the analysis and visualization of the dataset, the identified proteins were organized in four groups: unique in hES, shared with an enrichment in hES, with an enrichment in OKSM 48h and unique in OSKM 48h (Fig. 3.14-3.18). Images shown were derived from the Cytoscape network described in Fig. 3.9b, which includes proteins that have been connected based in literature evidence. Additionally, for each group pathways and complex enrichment using ConcensusPathDB was applied to categorize the proteins in each group, indicating in boxes the most enriched processes and the proteins involved.

In the following sections, the findings for each group will be discussed.

3.4.3 OCT4 unique chromatin-bound partners in hES are associated with pluripotency maintenance

When mouse and human OCT4 interactomes were compared, the OCT4 interactome described in hES contained most of the main proteins of the core pluripotency maintenance network (Fig 3.5). As expected, when the proteins described as unique or enriched in hES when compared to OSKM 48h were indeed pluripotency protein members (Fig. 3.15, 3.16). As most of these proteins are stem cell specific proteins, their enriched or exclusive interaction with OCT4 in hES and not early reprogramming indicates that their interaction with OCT4 occurs in the later stages of reprogramming, when most these proteins start to get expressed (SILAC)(Fig. 3.13) [105].

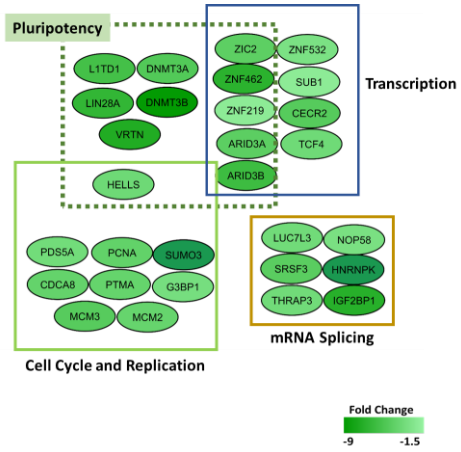


Fig. 3.15 OCT4 hES unique interactions. Subset of proteins identified only in pluripotency. Boxes denote and their associated biological process. Green dotted box includes proteins associated to the pluripotency network according to the literature. Colour coding represents the level in abundance of each protein (fold change).

Besides the already well stablished pluripotency associated proteins, the unique hES chromatin associated proteins included proteins which functions in either reprogramming or pluripotency maintenance have not been fully elucidated. Examples of these proteins included CERC2 (histone acetyl-lysine reader), ZFP462 (zinc finger involved in chromatin stability), CBX5 (heterochromatin protein), zinc protein fingers (ZNF198, ZNF219, ZNF281, ZNF462, ZNF532), HELLS (chromatin remodeller) and HMGA2 (histone-DNA modifications). Interestingly, ZNF532 and ZNF219 have been described in cancer gene-fusions involved in the formation of unusually large domains of hyperactive chromatin by deregulating acetylation [261, 262]. Therefore, their presence in the

OCT4 interactome of hES could suggest a potential role ZNFs proteins along with OCT4 in chromatin structure and regulation of gene transcription during pluripotency.

On the other hand, mRNA processing, splicing and cell cycle associated-proteins were also present in both the unique and enriched group of hES interacting proteins (Fig. 3.15, 3.16). Some of these proteins have been reported to have positive effects when overexpressed in reprogramming. For example, addition of the RNA binding protein LIN28A in the reprogramming cocktail accelerates reprogramming efficiency in a proliferation-dependent manner by mechanisms still not fully understood but that could be linked to its capacity to interact with OCT4 [241].

Overall, the unique and enriched OCT4 interacting proteins in hES confirmed the involvement of OCT4 with the well stablished core pluripotency network. Additionally, they allowed the identification of new proteins that once characterized in pluripotency could be potential candidates to test in the reprogramming process (Fig. 3.14, 3.15).

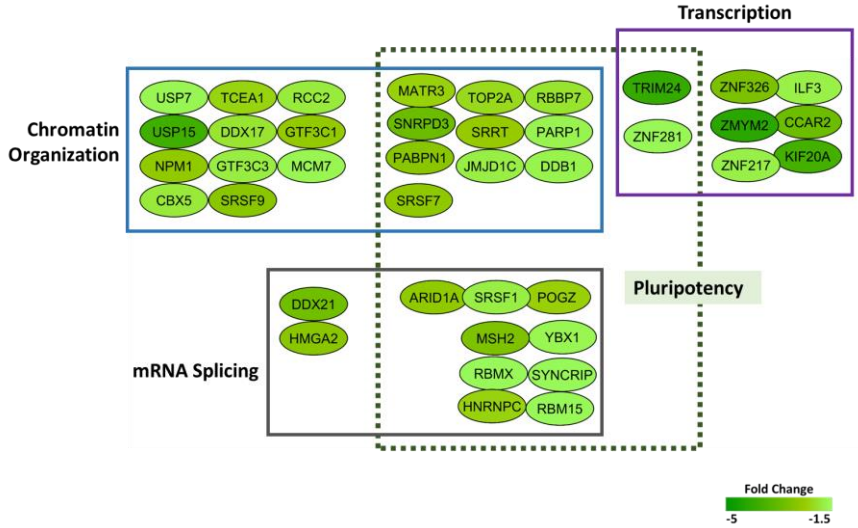


Fig. 3.16 OCT4 hES and OSKM 48 shared interactions enriched in hES. Subset of proteins identified in both pluripotency and early reprogramming enriched in hES. Boxes denote and their associated biological process. Green dotted box includes proteins associated to the pluripotency network according to the literature. Colour coding represents the level in abundance of each protein (fold change).

3.4.4 OCT4 acquires novel chromatin-bound associated proteins during early reprogramming

The most interesting group when comparing hES and OSKM 48h was the set of proteins that were only present at the early stages of reprogramming (Fig. 3.17). Quantitative

analysis of this group of proteins in hES and HF suggested OCT4 new interactions were not exclusively determined by the gene expression or protein levels of the interactors in each condition (hES or OSKM 48h). For instance, there were a set of proteins with higher expression in hES when compared with HF, but more enriched in the OCT4 interactome at OSKM 48h versus hES, revealing that, for some of the novel OCT4 interactors in OSKM 48h, their expression levels in either cell type did not correlate with the enrichment levels observed in the reprogramming OCT4 interactome.

Enrichment analysis of this group of proteins revealed a lesser amount of proteins involved in pluripotency maintenance and more proteins involved in differentiation and developmental processes, as well as chromatin structure and transcription regulation (Fig. 3.17). This suggests that proteins involved in differentiation pathways can contribute to the reprogramming through their association with OCT4 and suggest common mechanisms for cell differentiation and reacquisition of pluripotency, with OCT4 as an important component. Interestingly, most of the proteins included in this group have not been found to be linked with OCT4 nor described in the reprogramming process, highlighting that the existing barrier in the understanding of OCT4 roles in reprogramming. A set of worth noticing proteins found in this group, are somatic specific transcription factors that have been reported to be downregulated in MEF reprogramming, such as HOXC10, RUNX1, FOSL1 and TAGLN [154, 263, 264]. The downregulation of these somatic transcription factors is believed to contribute to the downregulation of the somatic genes at early reprogramming. How the OSKM are regulating the repression of these specific genes is not yet fully understood, but evidence suggests that at 48hrs of OSK induction in MEFs, the OSK factors share binding sites with RUNX1 and FOSL1. These binding sites include MEF enhancers important for the somatic gene regulation [154]. Detection of FOSL1 and RUNX1 as OCT4 chromatin-associated proteins supports the evidence that they co-bind in the genome at early stages (Fig. 3.16). Interestingly, in the study previously mentioned also reported that OSK induction drives the redistribution of these transcription factors to other genomic regions [154]. This mechanism could suggest that OCT4 binds to somatic enhancers competing with the somatic TFs already bound, resulting in their displacement and further recruitment of chromatin remodelling machinery by OSK to close and repress the somatic enhancers [154]. Alternatively, these new somatic TF-OCT4 interactions do not rule out the

possibility of a synergistic function in which, before their downregulation, the somatic TF take part of transient complexes important for reprogramming, even if they are active in a short timeframe.

Taking into account the most abundant proteins identified in the unique OSKM 48h interactome, two members of the Nuclear Factor I family, NFOC and NFIX were identified (Fig. 3.17). These proteins are site-specific DNA binding proteins involved in a large variety of cellular and viral genes. Their binding to DNA promotes the transcriptional activation or repression, depending on the cellular context and the regulatory region where they bind [265]. Binding sites for the members of this family have been identified in promoters, enhancers and silencer regions of a huge set of genes that are expressed in almost every tissue [266]. More recently, they were described as key epigenetic regulators and chromatin remodelers during development and cancer [265], opening the possibility of a new non-described OCT4/NFIC/NFIX complex involved in chromatin remodelling and transcriptional regulation at early stages of the reprogramming.

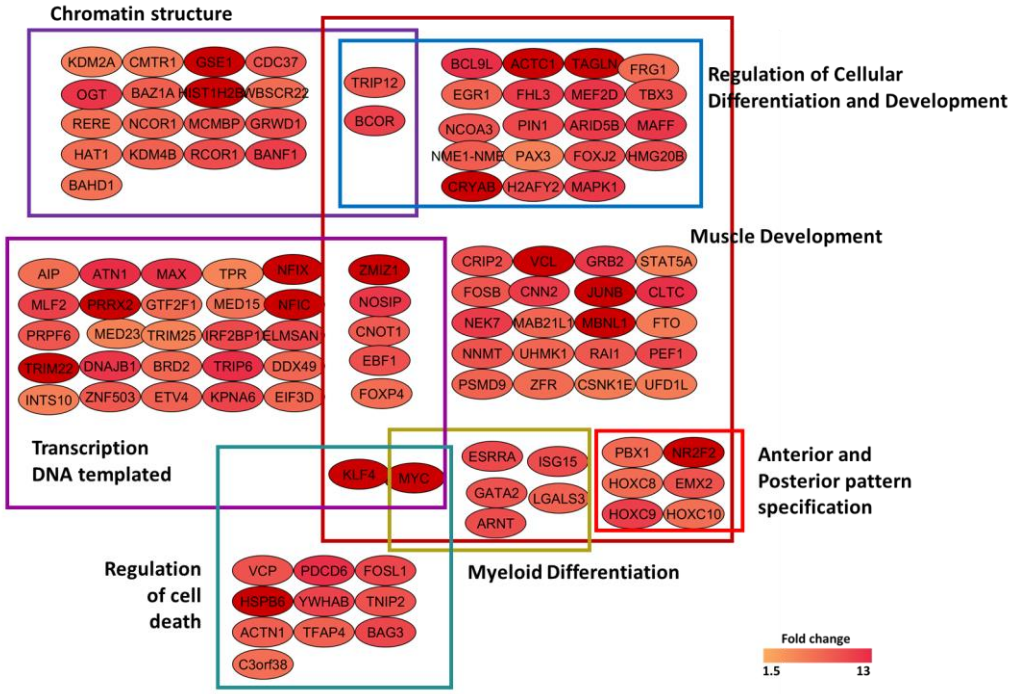


Fig. 3.17 OCT4 OSKM 48 unique interactions. Subset of proteins identified only in early reprogramming. Boxes denote and their associated biological process. Colour coding represents the level in abundance of each protein (fold change).

Another interesting group of proteins found in the unique OCT4 OSKM 48h subset were three proteins belonging to the Homeobox C cluster (HOXc8-10) (Fig. 3.17). Hox proteins are transcription factors involved in controlling and coordinating morphogenesis with established functions in development and evolution, including DNA replication, DNA repair, mRNA translation and protein degradation [267]. The Hox family in humans includes 39 members, with high relevance not only because of their roles in development, but also because they have been involved in several diseases, such as different types of cancer[267]. Evidence of their expression during reprogramming has been described. Moreover, it was also found that an early wave of gene expression change involved the reactivation of late developmental regulators, such as members of the Hox genes [264]. This suggested that these genes are somehow involved in the process; therefore, their interactions with OCT4 could help define their role in the process. Since reprograming somatic cells to stem cells could be described as a forced reverse developmental process, understanding the interactions of Hox genes with the OSKM factors and how they are involved in this transition could be of high relevance.

Furthermore, the identification of this new group of proteins –not previously associated with OCT4 either in reprogramming or other cellular contexts –demonstrates that OCT4 gains new chromatin associated proteins from the early stages of reprogramming, proving that the initial engagement of OCT4 with the somatic proteome on chromatin differs from that during pluripotency maintenance. This is consistent with the evidence that the initial engagement of OCT4 with the somatic human genome was also markedly different from that in hES (Fig. 3.10) [110].

3.4.5 Involvement of OCT4 in chromatin organization complexes is fundamental in early reprogramming and pluripotency maintenance

The unique proteins identified in each group, helped understand particularities of both, pluripotency and reprogramming. Furthermore, an interesting subset of shared OCT4 interactors in both OSKM 48h and hES (Fig. 3.18). Included in this list of proteins were the majority of the proteins part of the SWI/SNF, LARC and Drosha complex discussed before when comparing hES and mESC interactomes (Fig. 3.5).

The fact that these complexes are present in both conditions is a major finding that reflects that both processes share similar mechanisms to regulate chromatin-structure and miRNAs taking advantage of OCT4 as one of their subunits, either by recruiting the complex or being recruited by the complex. As in pluripotency maintenance, SWI/SNF has been described to be a cofactor for reprogramming [235], but it is not yet clear how both processes are taking advantage of the same mechanisms; either by using them for similar functions, or using them as a scaffold for additional proteins with a more specific role for each process to bind. Examples of the latter have been previously described involving the Mdb3-NURD stem cell complex. In this complex the specific combination involving Mdb3 is necessary for pluripotency maintenance and reprogramming [121]. In addition to Mdb3, there has been other reports suggesting more stem cells specific SWI/SNF combinations, in which the complex has the potential to interact with ES cell-specific regulators, such as some of the unique proteins identified in the hES interactome (HELLS, SOX2, SALL4 and DNMT3B)[117]. As SWI/SNF is a fundamental chromatin remodelling complex, it would be interesting to characterize specific combinations needed for early and later stages of reprogramming, unravelling a more specific role of specific SWI/SNF complexes at different stages of reprogramming.

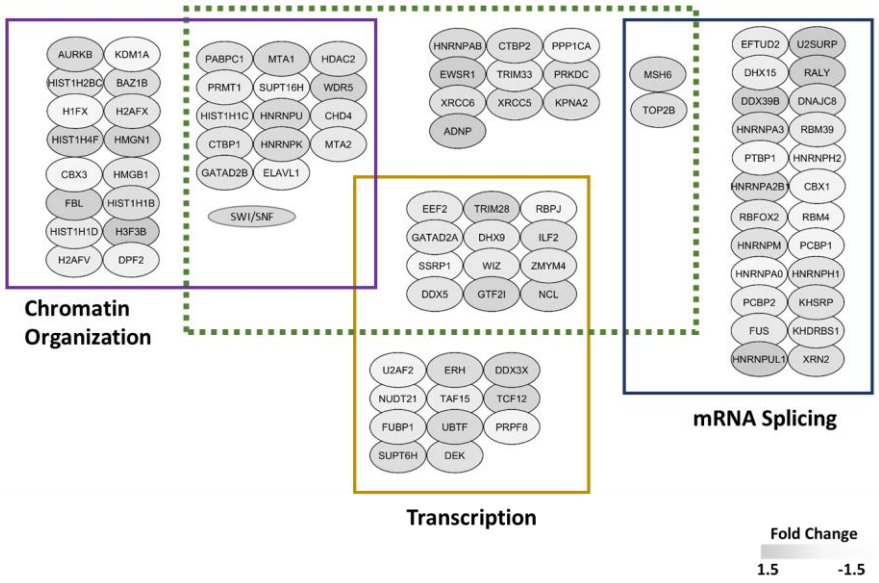


Fig. 3.18 OCT4 hES and OSKM 48 shared interactions with no enrichment difference. Subset of proteins identified in both pluripotency and early reprogramming with no difference in abundance between both processes. Boxes denote and their associated biological process. Green dotted box includes proteins associated to the pluripotency network according to the literature. Colour coding represents the level in abundance of each protein (fold change).

3.4.6 Enriched OCT4 interactions at early reprogramming include mechanisms involved in pluripotency maintenance

Enrichment analysis helped to define a group of shared proteins between hES and OSKM 48h with higher abundances in early reprogramming (Fig. 3.9, 3.19). Included in this group are proteins involved in the Wnt and Notch signalling. Among these proteins, three members of the co-repressor family TLE/Groucho were present (TLE3-5). These proteins are non-DNA binding co-factors and are key mediators of embryonic segmentation, dorsal-ventral patterning, neurogenesis, and Notch and Wnt signalling [268]. Because by themselves they cannot bind DNA, they require the interaction with transcription factors or DNA-binding proteins to mediate their repression activity. When bound to their target, these proteins can repress transcription by a diverse set of mechanisms including recruiting histone deacetylases (HDAC), chromatin condensation via physical tethering of histone tails and attenuating the transcription by polymerase pausing [268]. Due to their link with the Wnt signalling, the TLE family has been linked to mouse differentiation and development, where it is required to silence the expression of the pluripotency maintenance network in differentiation towards multiple lineages, which might be possible through its binding to inactive TCF3, a key transcriptional activator in the Wnt signalling in mESC [269]. Even though, the TLE family are key regulators of development their association with OCT4 has not been described in neither development nor reprogramming. However, an interesting mechanism described for other pioneer factors might link the enrichment in chromatin of TLE corepressors with OCT4 at early stages of reprogramming. This mechanism involves the recruitment of co-repressors by pioneer factor to establish stably silenced domains instead of the positive regulation of gene expression [36]. An example is the recruitment of TLE3 to specific genomic targets mediated by the pioneer factor FoxA. When recruited by FOXA, TLE3A causes the local chromatin to close rather than open, by condensing nucleosomes in the vicinity [37]. This mechanism suggest that pioneer factors, could be recruiting corepressors such as TLE keep the silent state of their targets, protecting against immediate and inappropriate gene activation. OCT4 could be taking advantage of this mechanism at early stages of reprogramming by maintaining a competent state ready for the binding of co-factors that promote the release of the TLE repressors to initiate the chromatin remodelling and transcription reactivation once required. As exemplified with the TLE proteins, the

remaining proteins included in this enriched OSKM 48h interactors could be revealing that OCT4 is taking advantage of some pluripotency mechanisms by enhancing them in early reprogramming to help drive the process.

Additionally, proteomic quantitative analysis using SILAC helped to rule out the possibility that the observed differences in proteins and their abundances were exclusively driven by the different proteomic expression profiles of somatic and stem cells (Fig. 3.13, 3.14).

The results presented in this chapter are the first report to define the OCT4 chromatin-associated partners in human stem cells and in early stages of the human reprogramming process. Comparison of these networks offered a dataset that allow a general and descriptive comparison for a better understanding of the differences of OCT4 and its interacting proteins in the pluripotency maintenance versus the reprogramming process in the human context. General analysis of both network revealed that OCT4 partners during early reprogramming and those in hESCs are markedly different. This evidence suggests that, as reported for the initial engagement of OCT4 with the somatic proteome, the OCT4 initial engagement with the somatic proteome on chromatin is distinct from that during pluripotency maintenance, illustrating how OCT4 is able to change its chromatin-binding dynamics in order to stablish different phenotypes. For instance, additional chromatin associated proteins reported in the hES interactome that have non-previously been described in the mouse pluripotency context could help understand and define the different pathways that govern human pluripotency and how they could be influencing the more primed pluripotent state observed in humans. On the other hand, OCT4 interactors that are exclusively enriched during early reprogramming included somatic transcription factors, supporting other studies that suggested OCT4 can redistribute these type of factors during reprogramming. Moreover, the list of new OCT4-interacting proteins non-previously reported in the reprogramming context (such as proteins involved in cell death, development and differentiation) represent a new dataset that could contribute to the better understanding of the early stages of the reprogramming process. However, it should be noted that the data presented in this chapter represents a general and descriptive overview of OCT4 interacting proteins, which could not reflect functional importance in either process, pluripotency or

reprogramming. Thus, further assays focused in the characterization of OCT4 interactors that are functionally relevant for reprogramming and pluripotency should be addressed.

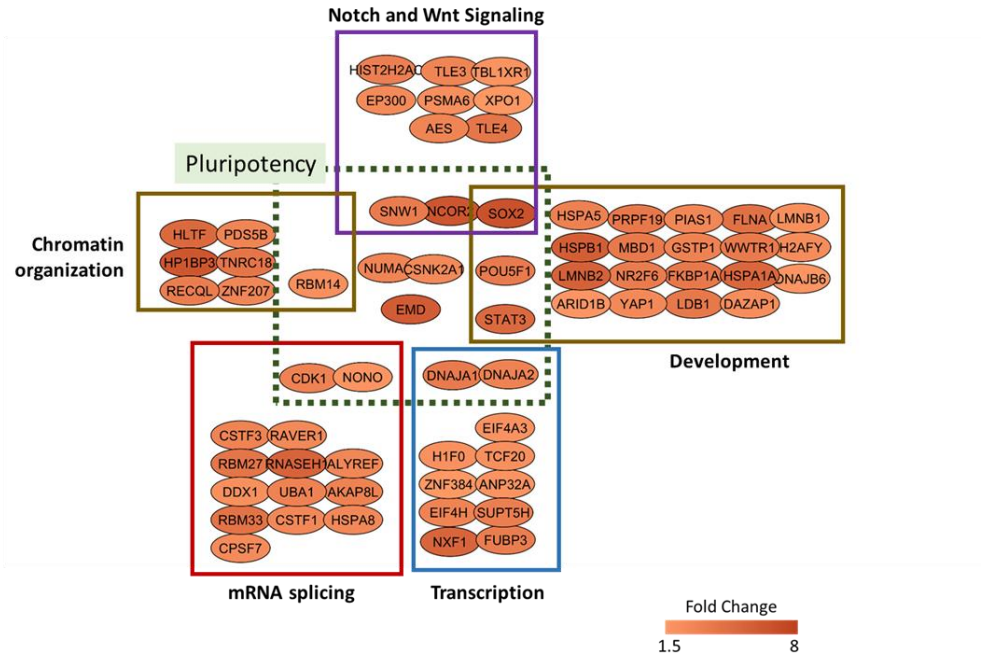


Fig. 3.19 OCT4 hES and OSKM 48 shared interactions enriched in OSKM 48h. Subset of proteins identified in both pluripotency and early reprogramming enriched in OSKM 48h. Boxes denote and their associated biological process. Green coloured box includes proteins associated to the pluripotency network according to the literature. Colour coding represents the level in abundance of each protein (fold change).

Chapter 4 OCT4 DOMAINS UNVEILED CHROMATIN-DEPENDENT PROTEIN INTERACTIONS NECESSARY FOR REPROGRAMMING TO iPSCs

4.1 Introduction

A basic feature of transcription factors is that they are modular proteins with functionally independent domains. While they depend on their DNA binding domains (DBD) to recognise specific DNA sequences, the activation or repression of gene transcription is usually achieved through interaction with other co-factors via domains that are located outside, and act independently of DBD [270].

OCT4 comprises three domains: a central POU domain flanked by an N-terminal and a C-terminal transactivation domain (TADs)[163]. The central DBD is a bipartite POU domain containing POU specific (POU-S) and POU homeodomain (POU-HD) separated by a linker containing a rigid helix and a flexible region. This domain allows the recognition of a specific octameric (OCT) DNA sequences and is highly conserved among species. Because of its importance in DNA binding, this domain has been widely studied and has been directly implicated in reprogramming to iPSCs and pluripotency maintenance [84, 217, 271]. Contrastingly, the N- and C-terminal TADs are responsible of the interaction of OCT4 with partner proteins (Fig. 1.4, Fig. 4.1a) [163].

The two OCT4 TADs have been shown to act redundantly in ESCs, as OCT4 containing the POU domain with either of TAD is able to maintain pluripotency but OCT4 mutants lacking both N- and C-terminal domains fail to maintain self-renewal [272]. Additionally, OCT4 TADs are intrinsically disordered and have been associated with transcription regulation activity because of their capacity to form phase-separated condensates with the co-activator Mediator complex MED1, which is a necessary mechanism to drive gene activation [8, 9].

More recently, a study performed in parallel in our laboratory, focused in the dissection of the OCT4 domains that are essential for reprogramming to iPSCs from the ones essential for pluripotency maintenance. By systematically deleting five amino acid stretches of OCT4 and screening them for reprogramming to iPSCs and pluripotency maintenance functions in mouse, this work found that reprogramming to iPSCs requires

defined polypeptide stretches within OCT4, which are distinct from those that maintain pluripotency in mESCs. Based on these regions essential and non-essential regions of OCT4 for reprogramming were defined and different OCT4 mutants with deleted regions based in these classification were designed, resulting in different reprogramming to iPSCs efficiencies in mouse and human (Fig. 4.1b-c). Of interest were three mutants: a mutant where removing non-essential regions showed enhanced reprogramming to iPSCs (O lin95-117), being more significant in MEF reprogramming, a mutant where removing essential regions abolished OCT4 reprogramming to iPSCs activity (O lin29-42) and a functionally-minimum mutant lacking three non-essential regions without affecting reprogramming (O lin-min) (Fig. 4.1b). Furthermore, these three mutants retained the ability to maintain pluripotency, including the deficient O lin29-42, suggesting that defined patches or domains within the NT and CT regions are uniquely essential for reprogramming and that the lack of function in deficient mutants is not due to complete loss of protein functionality. Altogether, this data demonstrated that OCT4 reprogramming to iPSCs is not only encoded by OCT4 DBD but also requires defined functional elements within the TADs, which need to be fully characterized for a better understanding of the OCT4 reprogramming activity (Roberts and Özkan, submitted).

The discovery of defined functional regions illustrates that through different domains OCT4 is able to adapt in different cellular contexts. Integrating these results with the evidence presented in Chapter 3 that demonstrated that OCT4 initial engagement with the somatic proteome on chromatin is distinct from that during pluripotency maintenance, suggests that one of the mechanisms by which these functional domains contribute to reprogramming to iPSCs is through their importance in promoting or blocking specific protein interactions. However, these OCT4 protein partners are yet to be defined.

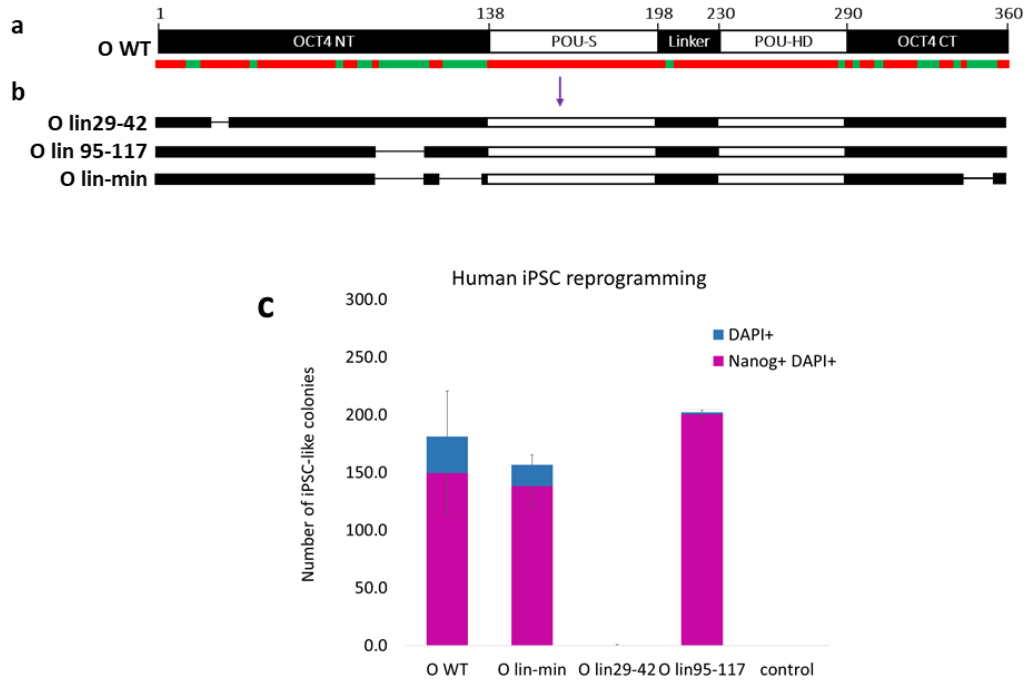


Fig. 4.1 Defined domains of OCT4 essential for reprogramming to iPSCs. a. Structure of the functional domains of hOCT4. Red-Green bars denote the essential and non-essential domains of OCT4 in mouse reprogramming. b. OCT4 mutants' structure illustrating the deleted regions. c. Reprogramming efficiency to human iPSCs of each mutants. Efficiency was quantified by counting the number of NANOG positive colonies (purple bars) versus DAPI colonies (blue bars) for each OCT4 deletion mutant in combination with SKM. Averages of at least three independent biological replicates are shown (error bars indicate ± s.d.). Images modified from (Roberts and Özkan, submitted).

The adapted ChIP-SICAP (Chapter 3) would be therefore perfectly suited to define how different OCT4 domains influence OCT4 engagement, while allowing the identification of important partners that are specifically required to induce pluripotency from differentiated cells. These essential reprogramming chromatin-associated proteins can then be targeted to better understand cell fate changes during reprogramming.

4.2 Aims

- Define chromatin-associated proteins that interact with OCT4 essential and non-essential domains in early reprogramming (OSKM 48h).
- Define essential proteins required for inducing but no maintaining pluripotency.
- Validate candidates by investigating their importance for reprogramming to iPSC.

4.3 Results

This results of this chapter are presented in three different sections. First, the chromatin-associated interactomes of OCT4 mutants in early reprogramming are identified using

the adapted ChIP-SICAP protocol. Next, the interactomes of the OCT4 wild type and mutants in early reprogramming to iPSCs and in pluripotency maintenance were compared to identify proteins important for reprogramming to iPSCs but not for pluripotency maintenance. Finally, the importance of these candidates were experimentally validated in reprogramming to iPSCs.

4.3.1 Defining the chromatin-associated proteins that interact with the essential and non-essential domains.

In order to identify if essential and non-essential domains deleted from OCT4 result lead to differences in the chromatin-associated proteins described in the dataset of WT OCT4 at early reprogramming and pluripotency in Chapter 3, the adapted ChIP-SICAP protocol was applied to the different OCT4 variants: O lin-min (OCT4 minimum with linker), O lin29-42 (OCT4 deficient mutant with linker) and O lin95-117 (OCT4 enhanced mutant with linker).

The ectopic expression of OCT4 mutants along with the SKM factors was induced in human fibroblasts (HF) for 48 hr, all resulting in similar cell morphological changes to those observed in OCT4 WT (Fig. 4.2a). Furthermore, each of the OCT4 mutants showed similar protein levels and were specifically recognized by the OCT4 antibody, as indicated by the intensity and the migration of the corresponding bands in Western Blot analysis (Fig. 4.2b). These results confirmed the expression of the OCT4 mutants early in reprogramming and the suitability of the antibody for further proteomics analysis. ChIP-SICAP protocol was then applied for each OCT4 mutant to identify their chromatin-associated proteins. First, samples were sonicated for 140 minutes, as previously established, showing optimal shearing profiles with an enrichment of 100-300 bp DNA fragments (Fig 4.2c).

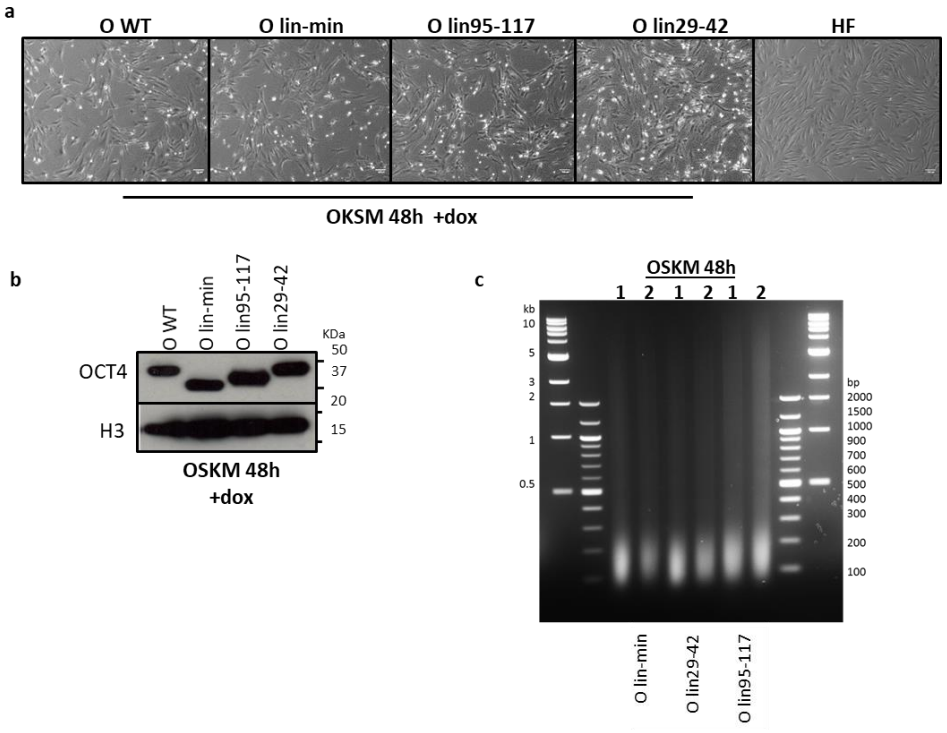


Fig. 4.2 Induction of OCT4 mutants and SKM factors. a. Images of non-transduced Human Fibroblasts (HF Control) and OSKM (WT and mutants) induced cells after 48 hours of dox addition. b. Western Blot analysis of each OCT4 mutant and WT after 48 hours of cell induction. c. Chromatin sonication of the OSKM 48h mutants used for ChIP-SICAP.

After carrying out the adapted ChIP-SICAP protocol and mass spectrometry analysis, the LFQ intensities of each protein were quantified and normalized against HF control (no OSKM) (Appendix Table 1). Considering proteins present in both replicates, a final number of 1207, 1065 and 684 proteins were identified for O lin-min, O lin95-117 and O lin29-42 respectively (Fig. 4.3a-c). Of these, OCT4 was among the top hits for all of them (Fig. 4.3 d-f). Even though the same amounts of OCT4 proteins and chromatin were used in the ChIP-SICAP experiments, the OCT4 mutants, especially O lin-min and O lin95-117 were enriched for a higher number of proteins as compared to O WT in early reprograming. Furthermore, this was even more than in hES (Fig. 4.4a). These differences may indicate that the deletions within the OCT4 mutants facilitate or stabilize the interactions of OCT4 with more proteins. GO analysis of each OCT4 mutant revealed the enrichment of nuclear proteins, as well as proteins involved in chromatin structure and transcription. This suggests that the increased amount of protein number was not a result of contamination of cytosolic or non-chromatin proteins (Fig. 4.4).

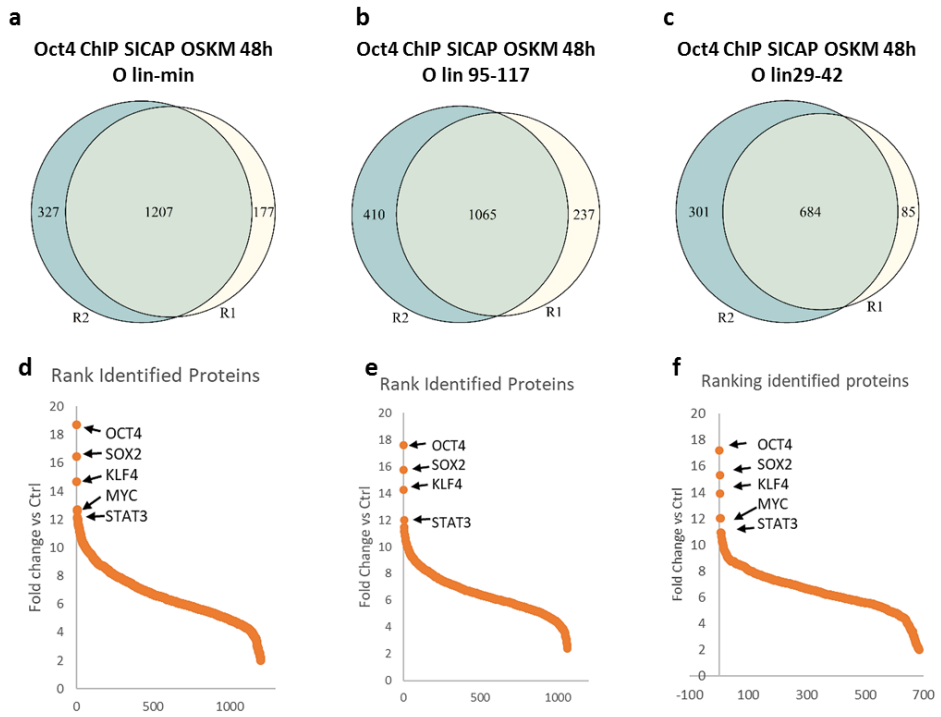


Fig. 4.3 Identified proteins by ChIP-SICAP for each OSKM 48h mutant. a-c Venn diagram of the intersection between both OSKM 48h mutants replicates and statistically significant against the control O lin-min (a), O lin 95-117 (b) and O lin29-42 (c). d, e and f. Identified proteins ranked by enrichment over control O lin-min (d), O lin95-117 (e) and O lin29-42 (f). g-i.

Overall, ChIP-SICAP protocol was successful in pulling-down and isolating the different type of OCT4 mutants and their chromatin-associated proteins in early reprograming, revealing, for the first time, a significant increase in the number of proteins that associate with mutated versions of OCT4 in chromatin in early reprogramming to iPSCs.

To gain a better understanding of the new properties acquired by the OCT4 mutants in early reprogramming, differential enrichment analysis was performed taking into account the quantification values for each protein. First, to get a high-level overview of the differences between OCT4 variants, PCA analysis was performed for all the OCT4 interactomes, including the negative controls. This revealed that the OSKM 48h samples clustered together, including WT and the mutants, while ES samples formed distinct a cluster (Fig. 4.4b). The negative controls also formed an independent cluster, despite different antibody and cell type being used, indicating common non-specific

contaminants. This analysis demonstrated that the differences between OCT4 WT interactors in early reprogramming and hES is greater than between OCT4 WT and the mutants in early reprogramming, despite the higher number of identified proteins for the OCT4 mutants.

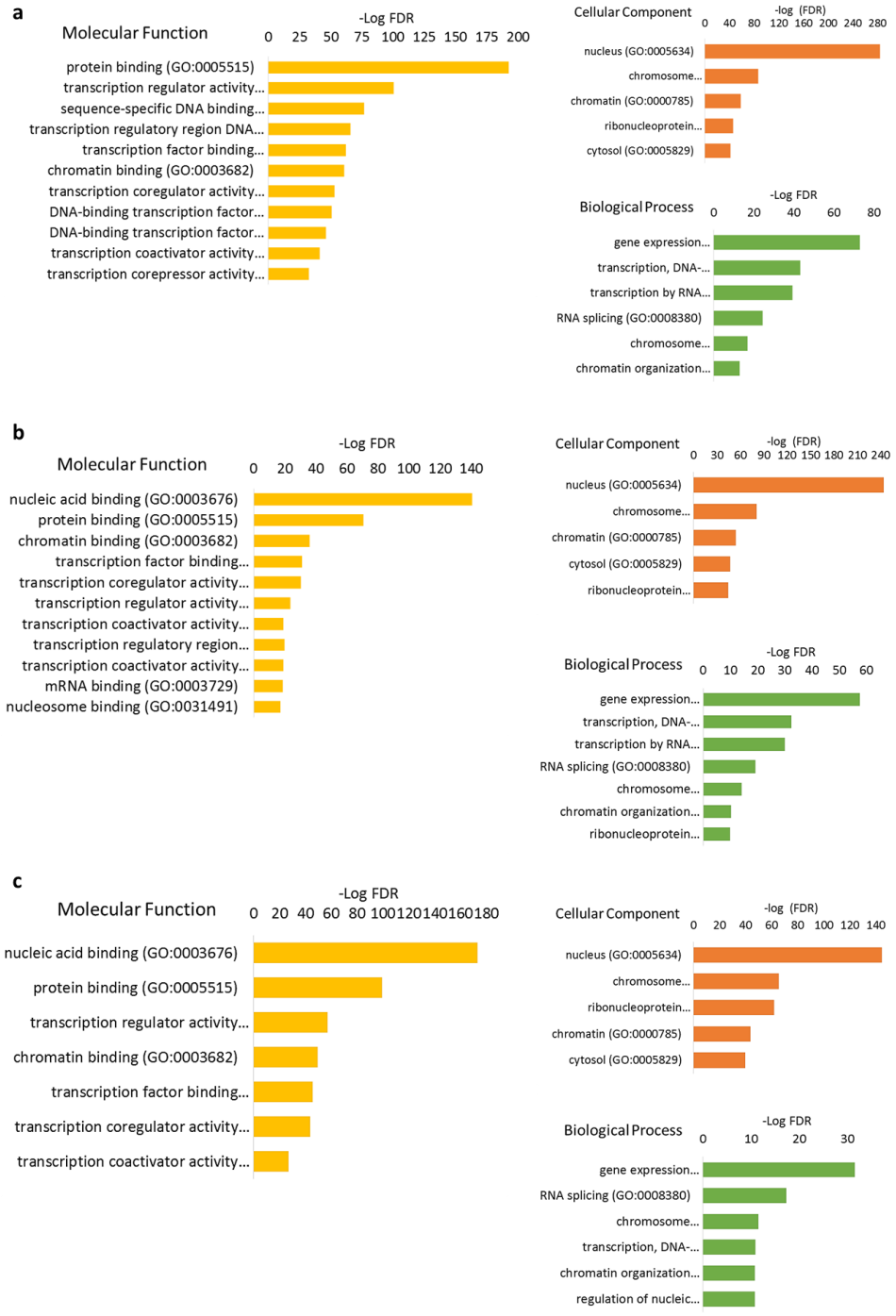


Fig. 4.4 Gene Ontology of identified proteins by ChIP-SICAP for each OSKM 48h mutant. a-c. Gene Ontology enrichment analysis for Cellular component, Biological Process and Molecular function of the identified proteins for O lin-min (a), min32 (b) and O lin29-42 (c).

To further address the differences and similarities between the interactomes a comparative analysis of shared and unique proteins was performed. The list of proteins to be compared was strictly restricted to proteins that were consistently present and absent in both replicates of all OCT4 variants. A total number of 725 proteins fit this strict criteria including 256 for hES, 370 for O WT, 469 for O lin29-42, 636 for O lin95-117 and 676 for O lin-min (Fig. 4.4c). More than 30% of the analysed proteins were present in all OCT4 interactomes, representing the biggest overlap, which was followed by the shared proteins between all OSKM 48h conditions (Fig. 4.5d). O lin-min was the mutant with most unique interactors (75) followed by O lin95-117 (21) and hES (13). Interestingly O lin29-42 interactors were all shared with the other interactomes. Therefore, the OCT4 interacting proteins found in both hES and all OSKM 48h are not sufficient to drive reprogramming, since even if O lin29-42 is able to bind them, it is still a deficient reprogramming OCT4 variant. Nevertheless, this set or shared proteins are necessary for the maintenance of pluripotency, as O lin29-42 does not lose its functionality to rescue and maintain pluripotency in mESC. Moreover, the remaining subgroups including the intersections between different OCT4 mutants and their unique interactors, reflect the properties gained by the OCT4 mutants to acquire new associations, increasing the differences and specific roles of OCT4 in early reprogramming compared to pluripotency maintenance.

Hierarchical clustering was then used to visualize and compare the relative intensity of the identified partners of each interactome (Fig. 4.6). The obtained heatmap allowed the classification of the proteins in 10 main groups: Group 1 included the proteins shared in all OSKM 48h (WT and mutants) and hES. Group 2 included proteins present only in O lin29-42 and O lin95-117; Group 3 included proteins present only in O lin95-117; Group 4 included the proteins present and in all OCT4 mutants and ES but no O WT; Group 5 includes proteins in all mutants but no ES or O WT; Group 6 included proteins only present in O lin-min; Group 7 included proteins present in O lin-min and O lin95-117; Group 8 included proteins present in all reprogramming to iPSCs mutants (O WT, O lin95-117 and O lin-min) but no in O lin29-42 or ES; Group 9 included proteins present in all OCT4 mutants (WT and mutants) but no ES, and Group 10 included proteins only present in ES.

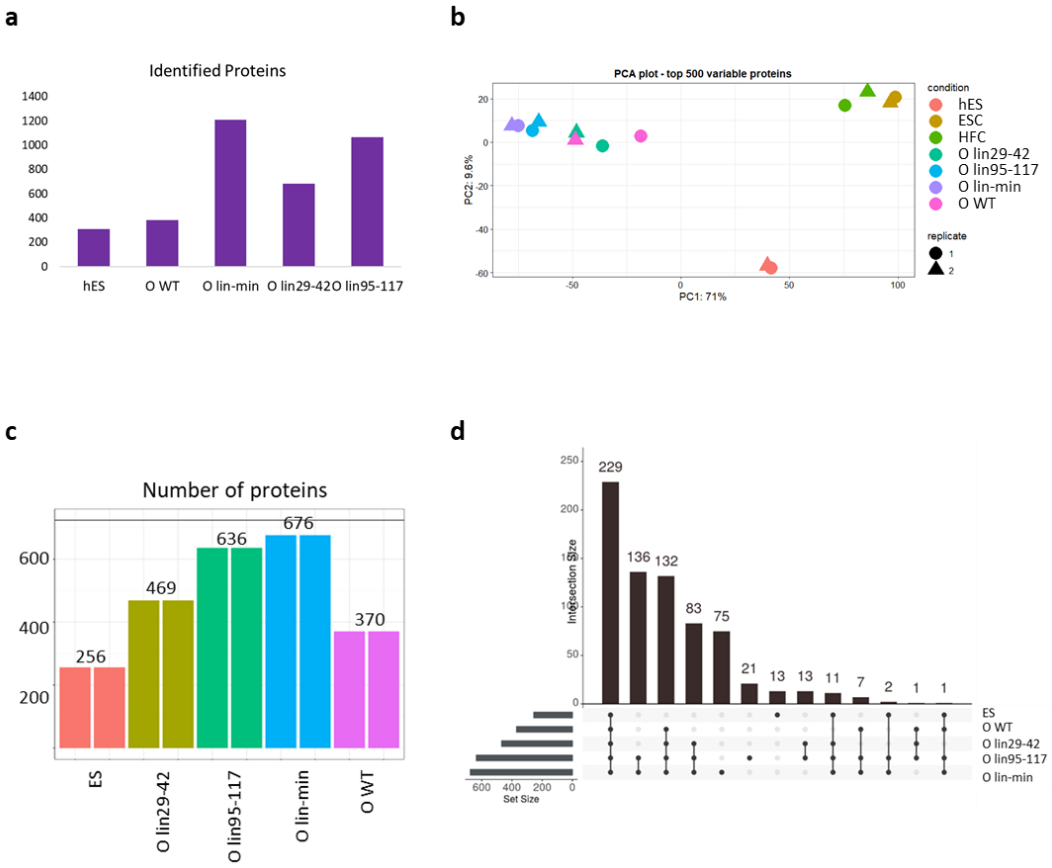


Fig. 4.5. Comparison of the expanded OCT4 ChIP-SICAP in pluripotency and reprogramming. a. Total number of proteins identified in each OCT4 ChIP-SICAP interactome hES and OSKM 48h (WT and mutants). b PCA score plot of total ChIP-SICP dataset obtained for hES and OSKM 48h (WT and mutants) including their respective controls. b. Total number of filtered proteins for each condition considered for future analysis. c. Upset plot illustrating the intersections between the shared and unique proteins identified in the OCT4 ChIP-SICAP of hES and OSKM 48h mutants.

Notably, one of the main differences observed was the increase number of proteins gained in the interactomes of the mutants (Groups 2,3,4,5,6,7. Fig. 4.6). More interestingly, for O lin-min and O lin95-117, although each mutant had their own unique set of proteins, most of the new interactions were shared between both mutants (Fig. 4.6 Group 7), which can be the result of both sharing a deletion fragment. Among these shared proteins were KDM2B, SMAD2, SMARCA2, PAX6 and ETV5 which have been previously associated with reprogramming [115, 235, 273-275]. It was also interesting to observe that even if O lin29-42 does not share a domain deletion with O lin95-117 or O lin-min, there was a notable overlap between the new gained interactors between these three mutants (Fig. 4.6 Group 5). This group includes proteins involved in transcription

regulation such as STAT6, PIAS3, KDM5B and proteins involved in cell cycle such as MAPRE1, CSNK2A2, MAD1L1, PPP2CB, NUP93, CCND1. Besides, another property of the mutants was that despite gaining more interactions, they were able to maintain most of the original interactors identified for O WT in early reprogramming and for the ones shared with OCT4 in hES, as represented by Group 1 and Group 9 (proteins discussed in Chapter 3). Group 1 included proteins that were previously reported in Chapter 3 to be shared in early reprogramming and pluripotency maintenance, including members of the NURD, SWI/SNF and Drosha complexes. Group 9 (Fig. 4.6) included the interactors that OCT4 gains in the reprogramming process and that were conserved by the mutants and had been previously described in reprogramming, including factors involved in chromatin structure such as ARID5B, HAT1, KDM2A, and development and differentiation processes such as STAT1, GATA2, MEF3D, EBF1, RUNX1 and JUNB. Most importantly, the mutants did not gain the specific stem cell OCT4 interactors included in Group 10 (Fig. 4.6) (SALL4, SALL2, DNMT3B, LIN28A, ARID3B, L1TD1, DNMT3A, ZIC2, CERC2 AND ZNF532, and VRTN AND HELLS).

Altogether, these results demonstrate that the removing the non-essential domains expand the interactome of OCT4 beyond the wildtype in early reprogramming. Particularly, O lin29-42 failed to reprogram fibroblast despite binding most of the proteins that also interact with WT, lin-min, and lin95-117 OCT4 counterpart, indicating there are key interactions missing. Interestingly, proteins within Group 8 included a small set of proteins that was not found in O lin29-42 interactomes, suggesting that loosing this set of partners detrimental for the reprogramming process.

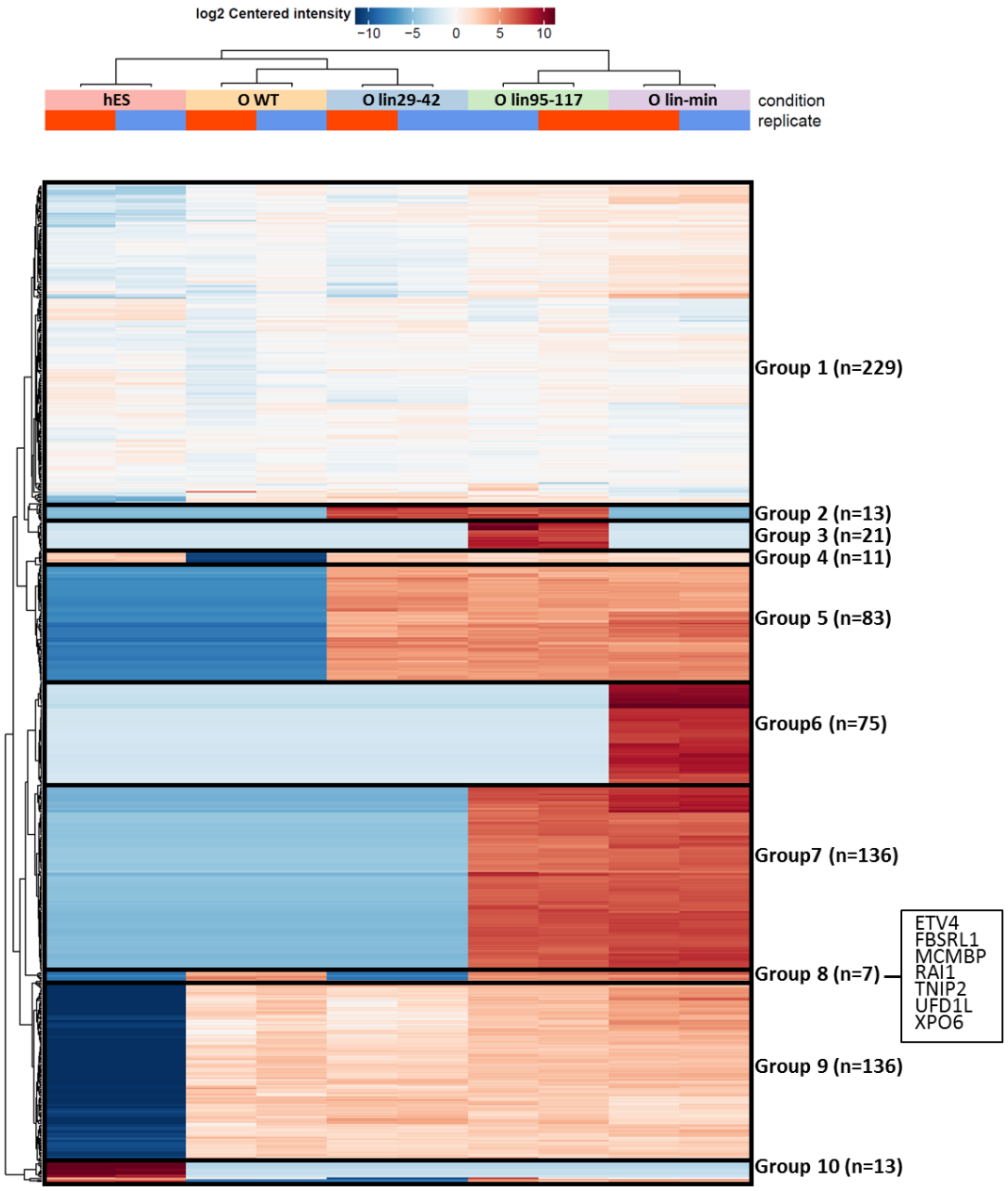


Fig. 4.6 Differential abundance of OCT4 chromatin-associated proteins in pluripotency maintenance and early reprogramming (WT and mutants). Hierarchically clustered heatmap of protein abundance pattern of filtered proteins identified for OSKM 48h (WT and mutants) and hES proteins. Samples are arranged in columns, proteins in rows. LFQ (abundance) intensities were log 2 transformed, centred and normalized. Red shades denote increased abundance, blue shades indicates reduced abundance (or absence). Manually defined groups are represented in the right. Each replicate is shown for each condition.

Overall, the general analysis between the interactomes of OCT4 chromatin associated proteins in pluripotency maintenance and early reprogramming (WT and mutants) defined that OCT4 gains new interactions when essential and non-essential domains are removed. This discovery could be reflecting new biological properties conferred by specific deletions, which grant OCT4 the ability to engage with more proteins involved in reprogramming, especially when deleting non-essential domains as seen with O lin-min. Most importantly, the intersection of the mutant interactomes with the OSKM 48h WT allowed the identification of a new OCT4 specific network in early stages of reprogramming not present in pluripotency maintenance, reinforcing the statement that in the reprogramming to iPSCs context, OCT4 gains new roles and engages different with the somatic proteome in comparison with the pluripotency maintenance one. Lastly, the differences observed between the mutants and WT OCT4 suggest that different domains of OCT4 confer different binding properties and lacking non-essential domains promotes different engagement with chromatin-associated proteins.

4.3.2 Essential OCT4 domains are necessary for its interaction with important reprogramming proteins

Clustering analysis reveal a set of proteins in Group 8, which included proteins missing in O lin29-42 interactome but present in the reprogramming variants of OCT4 (O WT, O lin95-117 and O lin-min) (Fig. 4.6). Seven proteins were included in this group: TNIP2 (TNFAIP3-interacting protein 2), RAI1 (Retinoic acid-induced protein 1), UFD1L (Ubiquitin recognition factor in ER-associated degradation protein 1), XPO6 (Exportin-6), MCMBP (Mini-chromosome maintenance complex-binding protein), and FBRSL1 (Fibrosin-1-like protein) (Fig. 4.7). Interestingly, these seven proteins were also missing in hES, meaning they could be representing a set of important proteins necessary for inducing but not maintaining of pluripotency. Moreover, apart from ETV4, which has been associated with mESC proliferation and differentiation [276], the rest of the proteins have not been previously directly linked in the reprogramming process. Thus, these new OCT4 chromatin-associated proteins might represent candidates with potential new functions in the reprogramming process, where they might be required for inducing but not maintaining pluripotency.

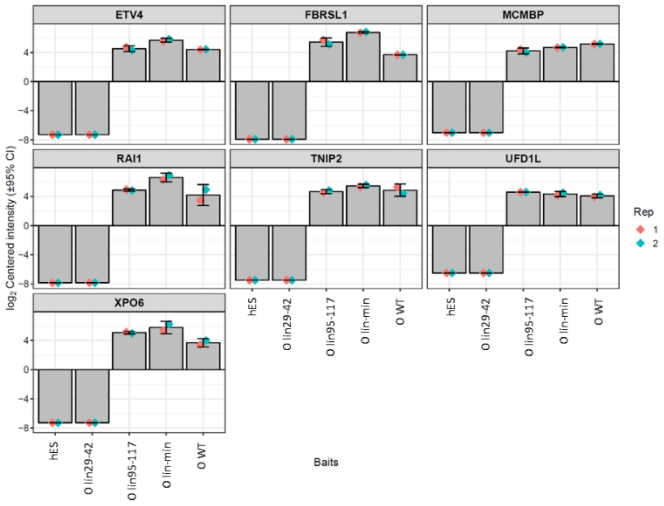


Fig. 4.7 Differential enrichment of candidates involved in the induction but not maintenance of pluripotency. Bar plots illustrating the enrichment of the candidate proteins across the different conditions. LFQ (abundance) intensities were log2 transformed, centred and normalized.

To investigate the functional necessity of these protein candidates in reprogramming, their encoding genes have been knocked out (KO) using CRISPR-Cas9 TNG MKOS Cas9 MEF. This secondary reprogramming system contains a dox-inducible MKOS + mOrange expression cassette, a GFP reporter and puromycin selection under the control of the endogenous Nanog promoter, as well as, a CAG promoter driven rtTA and a EF1a promoter driven Cas9 (Fig. 4.8a) This cell line has several advantages. First, reprogramming can be initiated by simply by adding dox to the media. Second, the expression of MKOS is coupled with mOrange, which can be monitored to help to identify partially-reprogrammed colonies. Third, NANOG expression can be detected by GFP to identify fully reprogrammed iPS colonies. Fourth and most importantly, the knockout of specific genes can be achieved by infecting the cells with lentiviruses encoding sgRNA against the gene of interest, resulting in insertion and deletion mutations (indels) by the constitutively expressed Cas9. Therefore, this system allows the efficient gene KO during reprogramming to iPSCs by the solely addition of dox to the ES media and the lentiviral transduction of the sgRNA of the gene of interest (Fig. 4.8b). This system has been successfully used to carry out a genome-wide loss-of function screen during iPSC reprogramming, identifying 23 genes that impede reprogramming and 1,921 genes that are essential for reprogramming (Kaemena and Beniazza *et al.*, submitted).

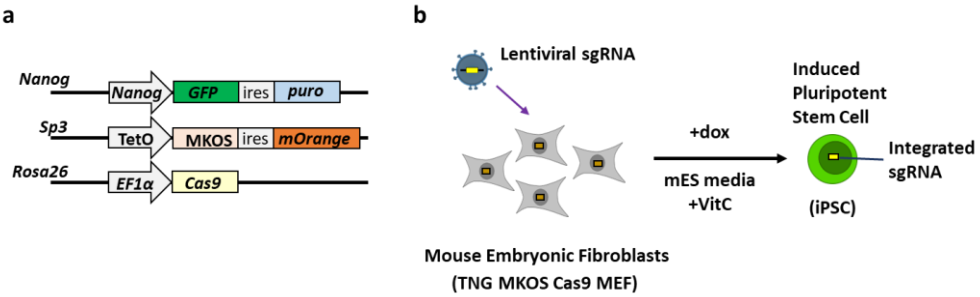


Fig. 4.8 TNG MKOS Cas9 MEF Reprogramming System. a. Representation of the TNG MKOS Cas9 MEFs transgenes b. Reprogramming scheme for MEFs reprogramming to iPSCs and the knockout of candidates. NANOG-GFP expression indicates fully reprogrammed iPSCs. Imaged modified from Kaemena and Beniazza et al., submitted.

To knockout the OCT4-interacting candidates in TNG MKOS Cas9 MEF, the sgRNAs sequences were obtained from the library used in the KO screen mentioned above, which contains sgRNAs to target 90% of the mouse genes. Based on the screen data, the best sgRNA for each candidate were picked and cloned into the sgRNA lentivirus vector, which also included a BFP reporter and the expression of the sgRNA was under the control of the human U6 promoter. The *Trp53* and *Dot1l* genes were used as controls of roadblocks as it has been reported that their absence improves reprogramming [116, 277]. *Stat3, Etv5* and *Kdm4b* were used as a control for essential genes as they have been reported to be important for the process and their absence decreases the reprogramming efficiency [112, 278, 279]. Zeo was used as an off-target sgRNA control as it has no target in the mouse genome. Lentivirus for each sgRNA (controls and candidates) were transduced in a co-culture of 10% of TNG MKOS Cas9 MEFs and WT feeder-MEFs. After 24 hours, reprogramming was initiated by changing to mESC media supplemented with dox and Vitamin C. After 15 days, whole well fluorescence imaging was performed with the Celigo cytometer (Fig. 4.9a). The *Mcmbp* and *Ufd1l* knockouts resulted in the most drastic decrease in Nanog-GFP positive colonies, similar to what was observed with the *Stat3* control, indicating that these genes are essential for reprogramming (Fig. 4.9b). Moreover, gene knockout of the remaining candidates *Xpo6, Rai1, Tnip2, Fbrsl1* and *Etv4* have also significantly decreased the number of Nanog-GFP colonies when compared with the sgRNA controls (*Zeo, Dot1l, Trp53)* and cells with no virus, although not to the same extent as *Mcmbp* and *Ufd1l* KOs (Fig. 4.9b). This therefore suggests that *Mcmbp*

and *Ufd1l* are essential for reprogramming, while the rest of the candidates may be important for driving more efficient reprogramming.

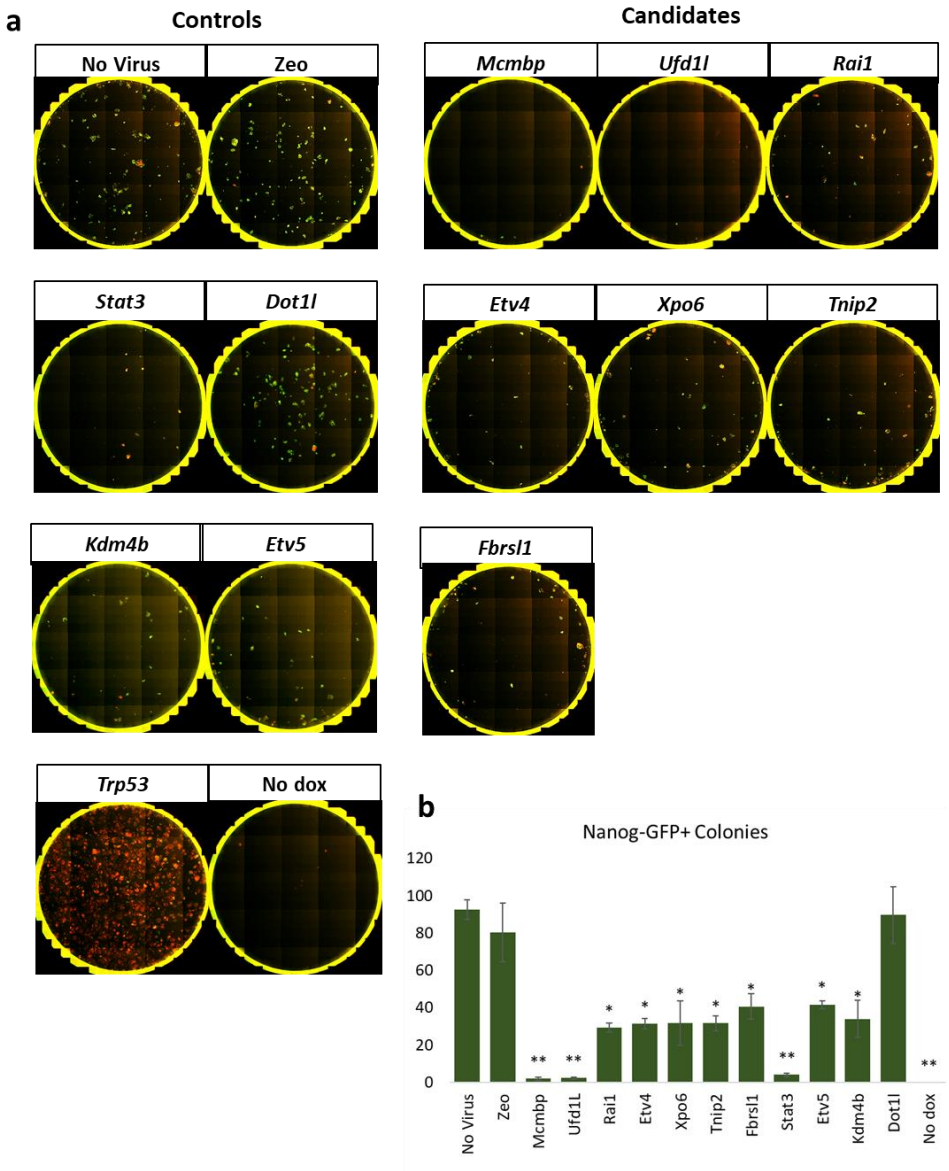


Fig. 4.9 Effects of candidate genes KO in TNG MKOS Cas9 MEF Reprogramming System. a. Whole well fluorescent images of MEF reprogramming at Day 15. One representative well is shown for each candidate. GFP represent NANOG+ iPSCs. b. Reprogramming efficiency to mouse iPSCs after KO of each candidate. Efficiency was quantified by counting the number of GFP NANOG positive colonies. Averages of three replicates are shown (error bars indicate ± s.d.). ** p.value<0.01. * p.value<0.05.

After establishing that the knockout of all candidates had negative effects in reprogramming to iPSCs, their over-expression may have the opposite effect and contribute positively to the process. To investigate if this was the case, the candidates

were overexpressed using a dox-inducible lentivirus system in the same cell line (TNG MKOS Cas9 MEFs) but without the KO and the sgRNAs (Fig 4.10).

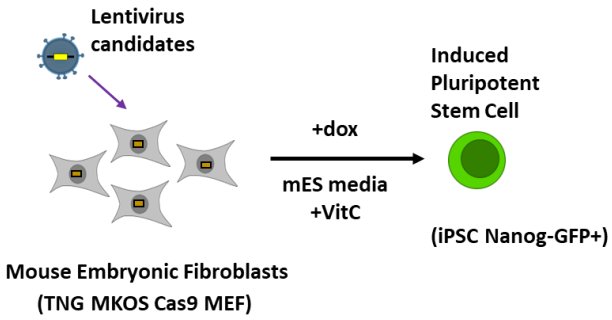


Fig. 4.10 TNG MKOS Cas9 MEF Reprogramming System and overexpression of the candidates. Reprogramming scheme for MEFs reprogramming to iPSCs and overexpression of the candidates. NANOG-GFP expression indicates fully reprogrammed iPSCs. Image modified from Kaemena and Beniazza et al., submitted.

DOX-inducible lentiviruses encoding for all candidates apart from *FBSRL1*were generated using ZBTB2 and KDM4B [280] that known to enhance reprogramming were used as positive controls. Next, MEFs (10% TNG MKOS Cas9 MEF and 90% WT MEFs) were infected with these viruses for 24 hr and reprograming was initiated by adding Dox along the induction of each ectopic candidate. After 15 days, whole well fluorescence imaging was performed with the Celigo cytometer, allowing the counting of Nanog-GFP colonies in three biological replicates (Fig. 4.11a-b).

As expected, ETV4 overexpression enhanced reprogramming by more than 2 fold, consistent with ETV5 overexpression in previous reports [276]. In contrast, overexpressing MCMBP, TNIP2, and UFD1L resulted in significantly less Nano-GFP colonies, indicating less efficient reprogramming (Figure 4. 11b). This suggests that the expression levels of these proteins is fundamental for a successful reprogramming to iPSCs, as their reduction or increase lead to negative effects in the process. No effect was observed when XPO6 and RAI1 were overexpressed, indicating that while normal levels of this proteins are needed to facilitate reprogramming, higher amounts has no additional contribution to the process (Fig. 4.11). In conclusion, these candidates play a crucial role for inducing reprogramming by a chromatin-mediated interaction with OCT4.

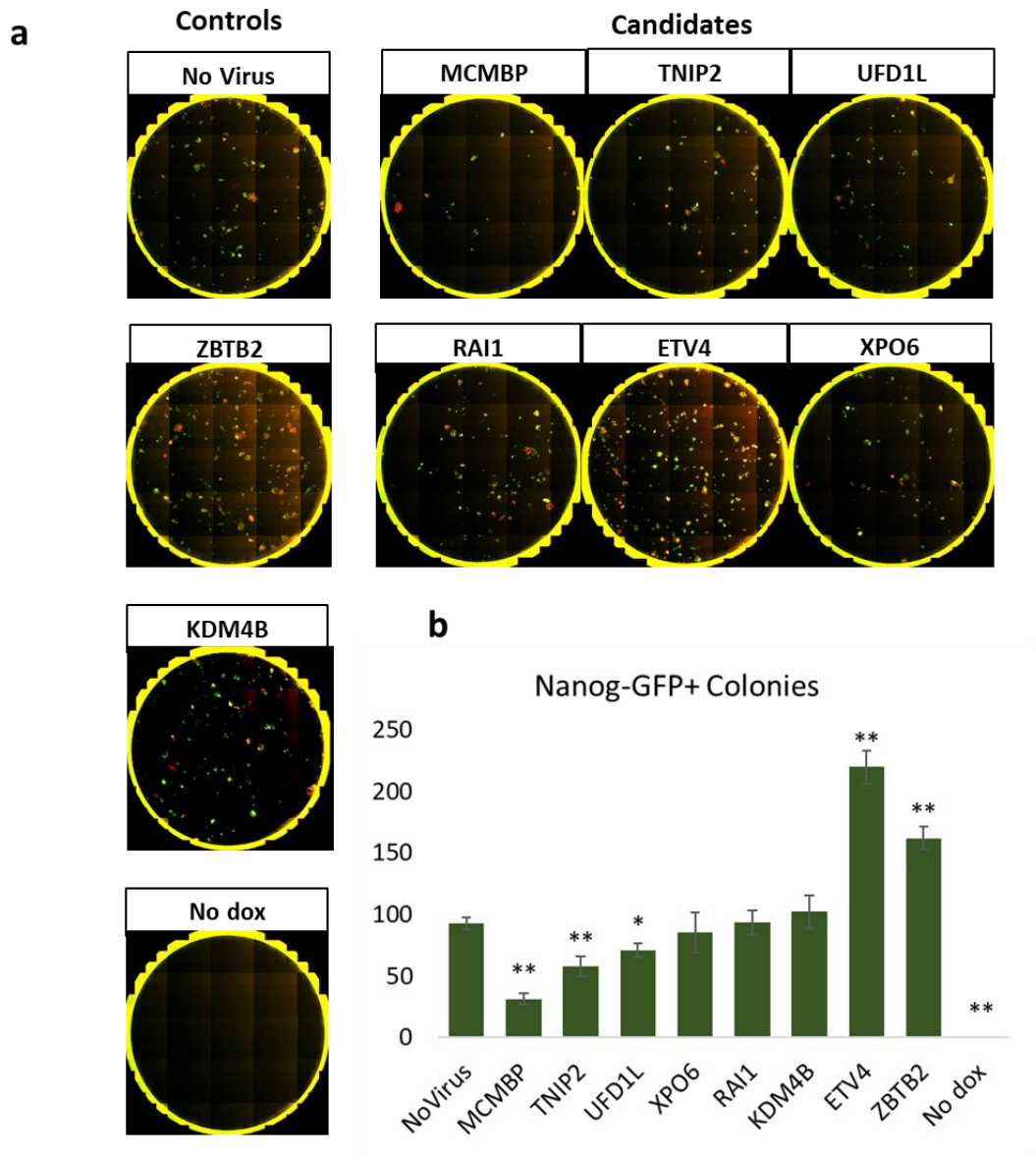


Fig. 4.11 Effects of candidate protein over expression in TNG MKOS Cas9 MEF Reprogramming System. a. Whole well fluorescent images of MEF reprogramming at Day 15. One representative well is shown for each candidate. GFP represent NANOG+ iPSCs. b. Reprogramming efficiency to mouse iPSCs after constitutive over expression protein of each candidate. Efficiency was quantified by counting the number of GFP NANOG positive colonies. Averages of three replicates are shown (error bars indicate ± s.d.). ** p.value<0.05. * p.value<0.1.

4.3.3 OSKM induction promotes the recruitment of important proteins to chromatin

To shed light on how the functionally validated OCT4 partners play important roles in reprogramming, changes in their chromatin enrichment were investigated. To this end,

proteins from the cytoplasmic, soluble nuclear (not associated with chromatin) and the chromatin fractions were isolated from hES, OSKM48h (OCT4 WT and mutants) and HF. Western blot analysis confirmed that the chromatin marker histone H3 was exclusively identified in the chromatin fraction while LaminB was found in the soluble nuclear fraction as well as chromatin, demonstrating the efficiency of the fractionation (Fig. 4.12a). OCT4 expression was also validated in hES and OSKM 48h (WT and mutants) showing expression in all the subcellular fractions and no expression in HF control (Fig. 4.12a). Detection of candidates and KDM4B as a control were tested in the chromatin fraction, with the exception of FBSRL1 and MCMBP and RAI1 due to the low quality of commercially available antibodies. When measured together (similar exposure), the extent of the ectopic OCT4 expression was very apparent as very high protein levels were readily detected in the chromatin fractions from OSKM 48h samples, while the endogenous OCT4 from hES was barely visible almost similar to that in non-infected HFs (Figure 4.12b, see figure 4.12a for optimally exposed endogenous OCT4). Remarkably, TNIP2 and UFD1L were more enriched in chromatin when overexpressing OCT4 WT and the reprogramming efficient mutants O lin95-117 and O lin-min but showed diminished chromatin association along the reprogramming-deficient O lin29-42 and in hES (Fig. 4.12b). These mutants were completely absent in the chromatin fraction of non-infected HFs, demonstrating that OCT4 is involved in loading and recruiting these two proteins chromatin only during successful reprogramming. Thus, the deficiency of mutant O lin29-42 for driving the reprogramming process might may be related to its inability to recruit these two proteins to chromatin. On the other hand, XPO6 and ETV4 showed more enhanced enrichment on chromatin with the overexpression of OCT4 WT and all mutants during reprogramming and in ESCs when compared to non-infected HFs. Therefore, while still important for reprogramming, the association of XPO6 and ETV4 with chromatin may also be driven by the other SKM factors and is not sufficient for the process.

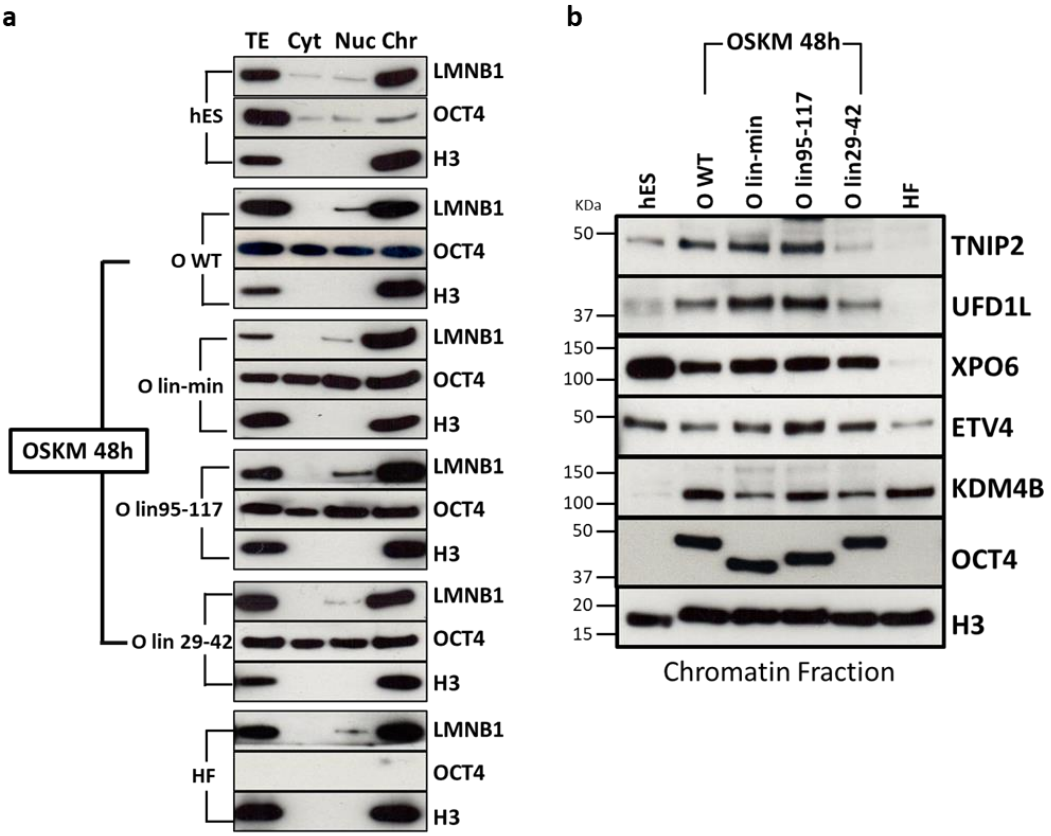


Fig. 4.12 Chromatin enrichment of candidates in human stem cells and human early reprogramming (OSKM 48h WT and mutants). a. Immunoblot detection of Histone 3 (H3), OCT4 and LaminB in hES, OSKM 48h (OCT4 WT and mutants) and HF control after a cellular fractionation procedure. TE= Total extract. Cyt = Cytoplasm, Nucl = Soluble Nuclear. Chr=Chromatin fractions. b. Immunoblot detection of candidate proteins and OCT4 in the chromatin fraction of hES, OSKM 48h (OCT4 WT and mutants) and HF control. H3 was used as a loading control.

In summary, the results of this chapter allowed expansion of the OCT4 interactome in OSKM 48h taking advantage of OCT4 mutants lacking essential and non-essential domains with different reprogramming efficiencies. Comparison of the interactomes of the OCT4 mutants along with WT OCT4 in early reprogramming to iPSCs and OCT4 in pluripotency maintenance showed that the deletion of essential and non-essential OCT4 domains results in and increase of OCT4 interactions with the chromatin-associated proteins in early reprogramming. Additionally, the analysis allowed the identification of seven non-previously described proteins important to induce but not maintain pluripotency. Characterization of these candidates demonstrated they are essential proteins for mouse reprogramming to iPSCs. Lastly, enrichment of the candidates in

chromatin suggested their recruitment to chromatin might be mediated or influenced by OCT4 when HF are induced with OSKM.

4.4 Discussion

OCT4 is a modular protein with functionally independent domains. A recent study developed in the Soufi lab, dissected the OCT4 domains that are essential for reprogramming to iPSCs from the ones essential for pluripotency maintenance (Gareth Roberts and Burak Özkan *et al.,* submitted). Different OCT4 mutants with deletions in these domains were designed; resulting in different reprogramming efficiencies, demonstrating that OCT4 reprogramming to iPSCs is not only encoded by OCT4 DBD but also requires defined functional elements within the TADs. The interesting particularities of these mutants included a deficient reprogramming variant, lacking an essential domain in the N-terminus (O lin29-42), an enhanced reprogramming variant lacking a non-essential domain in the N-terminus (O lin95-117) and a minimum OCT4 lacking three non-essential domains, two in the C terminus and one in the N-terminus. (Roberts and Ökzan, submitted).

For a better understanding of how the deletions were influencing OCT4 function in reprogramming (OSKM 48h), this chapter was focussed in characterising these mutants by defining their chromatin-associated partners by ChIP-SICAP at early stages of reprogramming, as it was demonstrated in Chapter 3 that the engagement of OCT4 with chromatin-associated proteins differs from its engagement in pluripotency maintenance. Interestingly, when compared with the interactomes of O WT in reprogramming and early pluripotency described in Chapter 3, these mutants revealed an increase in number of their chromatin-associated proteins (Fig. 4.3 and 4.5). This enhancement was not the result of unspecific interactions or non-chromatin associations, as mostly all of the previously described chromatin-associated proteins for O WT (OSKM 48h) were included in the interactome of the mutants and Gene Ontology revealed enrichment of nuclear proteins involved in chromatin remodelling and transcription regulation (Fig 4.3). For instance, O lin-min was the mutant with higher number of interactors, which could suggest that multiple deletions of non-essential domains provide a better conformation for OCT4 to associate with more proteins (Fig. 4.5). Interestingly, despite being able to bind more proteins, O lin-min does not have a positive nor negative effects in

reprogramming, evidencing that interacting with a higher number of proteins does directly leads to an improvement of the process. Correlating with this statement was the interactome properties observed with the deficient O lin29-42, which gain the same new interactors as O lin95-117 and O lin-min, but still was not functional for the generation of iPSCs (Fig. 4.5). This evidence indicates that although necessary, the shared proteins between O WT and the mutants are not sufficient to drive the process. Moreover, O lin29-42 did not gain any unique interactors but when compared with O WT (OSKM 48h and hES), O lin-min and O lin95-117, eight interactors were missing, from which seven were specific for the reprogramming process and not present in the OCT4 hES interactome: UFD1L, TNIP2, RAI1, MCMBP, XPO6, ETV4 and FBRSL1 (Fig. 4.6, 4.7). Functional assays of these proteins allowed the identification of seven new proteins not previously described in reprogramming that revealed to be important for the process, as their depletion by Knock Out (KO) decreased the reprogramming efficiency. Because of their importance for reprogramming, but their absence in hES interactomes, these new candidates can be classified as OCT4 chromatin-associated proteins necessary to induce but not maintain pluripotency and will be further discussed next.

4.4.1 OCT4 chromatin-associated proteins at early reprogramming can help unravel new mechanisms driving reprogramming

The identification of a subset of proteins important for the induction but not maintenance of pluripotency identified at early stages of the reprogramming process highlighted the importance of identifying and characterising the new interactions OCT4 is gaining as a reprogramming factor. Next, the OCT4 chromatin-associated protein candidates identified in this work will be discussed, combining the results of this study with previous literature reports to speculate their potential roles in the reprogramming process.

4.4.1.1 TNIP2

TNIP2 (TNFAIP3 Interacting Protein 2) also known as A20-binding inhibitor of NF-κB (ABIN-2) is classified as a cytoplasmic zinc-finger protein that functions as a negative regulator of NF-κB activation in response to multiple inflammatory stimuli [281]. Even though its expression and function had been mainly described in the cytoplasm, few studies suggest that the C-terminus is able to translocate to the nucleus and, when fused

with a DNA binding domain, activate expression of a reporter gene in human cells [282]. Although the mechanisms regulating its translocation to the nucleus and its specific role in the transcription regulation are not known, it has been associated to the member SMARCD1 from the SWI/SNF complex [282], RNA processing proteins like YMPL1 and nuclear ribonucleoprotein (RNP) structures, such as NONO, SFPQ and PSPC1 [283]. Interestingly, most of the proteins mentioned above were identified amongst the OCT4 interactomes with lowest enrichment in the deficient O lin29-42 and hES (Fig. 4.13). The presence of these proteins could link TNIP2 to different processes in the early reprogramming. Even when the mechanisms by which TNIP2 promotes transcription are still unknown, in early reprogramming it could be mediated by its interaction with SWI/SNF in the same genomic regions as OCT4, contributing to the transcription of essential genes. It might also be involved in the regulation of transcription to promote pluripotency through post-transcriptional regulation of mRNAs as it was reported TNIP2 can bind mRNAs [283]. Interestingly, most of the mRNAs it binds coded for transcription factors, including some that had been associated both positively and negatively in the reprogramming process, such as GATA2 [284], and JUN [149], respectively. It is possible that TNIP2 regulates these mRNAs in association with the paraspeckle proteins NONO, SFPQ and PSPC1, whose function include influence gene expression by controlling the nuclear retention or the mRNA transcripts [285]. It is worth mentioning that whichever mechanisms TNIP2 is involved in early reprogramming, it is highly dependent on a functional OCT4 when OSKM are induced, as significantly lower amounts of TNIP2 were observed in the chromatin fractions of OSKM 48h O lin29-42 (Fig. 4.12b). This evidence suggests a direct role of the essential domain of OCT4 missing in O lin29-42 for the enrichment of TNIP2 in chromatin, specifically when OSKM are induced. Additionally, a tight regulation of TNIP2 is necessary for a successful reprogramming process, as depletion and its overexpression both had negative effects in mouse reprogramming (Fig. 4.9 and 4.11). Lastly, the detection of TNIP2 in the chromatin fractions is the first evidence to demonstrate that TNIP2 not only can be translocated to the nucleus, but it can also be recruited to chromatin under exterior stimuli, such as the OSKM induction.

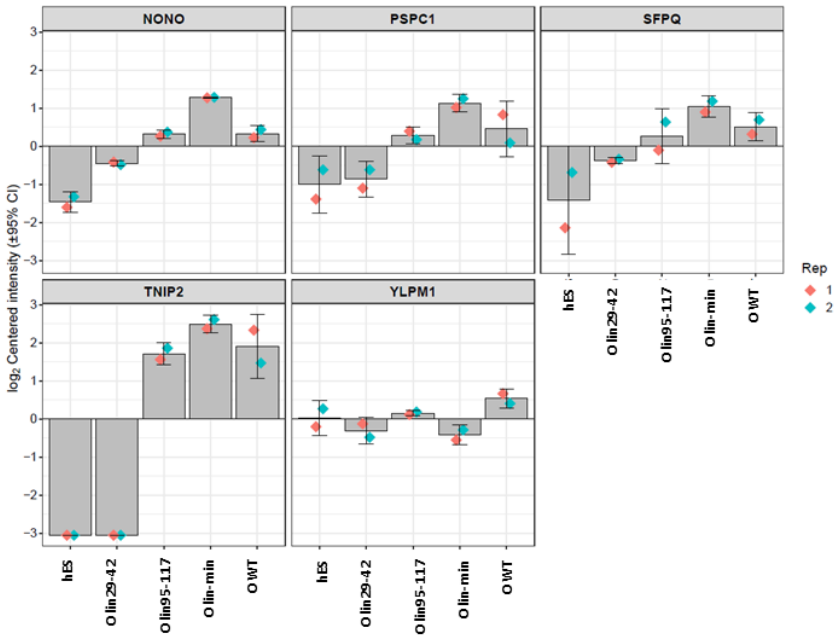


Fig. 4.13 Differential enrichment of RNA interacting proteins known to interact with TNIP2 that were identified in the interactomes. Bar plots illustrating the enrichment of proteins that had been described as interactors of TNIP2 (also shown). Proteins are shown for all conditions. LFQ (abundance) intensities were log2 transformed, centred and normalized.

4.4.1.2 UFD1L

Ubiquitin recognition factor in ER-associated degradation protein 1 (UFD1L) is an important component of the NPLOC4-UFD1-VCP complex involved in a degradation pathway for ubiquitin fused products (UFD) pathway [286]. In addition to UFD1L, the component VCP was also identified in all OSKM 48h (WT and mutants) and not in hES (Fig. 4.14), suggesting this complex might be present in early reprogramming. The complex main function is to recognize polyubiquitin tagged proteins and facilitate heir presentation to the 26S proteosome for protein degradation [286]. This is fundamental to restore protein homeostasis in the ER in response to stress result of accumulation of unfolded proteins [287]. Additionally, this complex is involved in the protein extraction of ubiquitinated proteins associated with chromatin which helps in maintaining genome stability as it was found that the inactivation of the subunit VCP leads to accumulation of ubiquitinated substrates on chromatin and results in protein-induced chromatin stress (PICHROS) [288]. PICHROS has negative effects in multiple DNA metabolic processes, including replication, damage responses, mitosis, and transcription, leading to genotoxic stress and genome instability [286, 288]. As UFD1L is an essential subunit of the complex,

the evidence presented in this work where its KO completely abolished reprogramming (Fig. 4.9) could be related to its involvement in PICHROS, as well as dysregulation of the ER stress response. On the other hand, ubiquitination dynamics are a fundamental posttranscriptional regulation of OSKM during reprogramming and pluripotency substrates [289]. For instance, OCT4 stability and turnover can be regulated by ubiquitination and sumoylation modifications [289, 290]. Evidence of SUMO and UBE proteins found in the OCT4 interactomes suggest this mechanism is part of OCT4 regulation (Fig. 4.14).

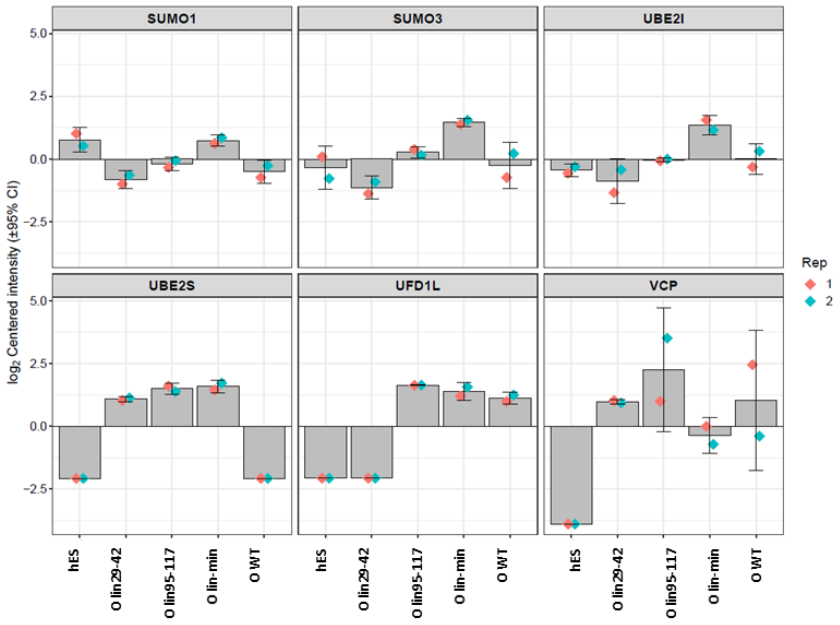


Fig. 4.14 Differential enrichment of VCP and UBE and SUMO proteins that were identified in the interactomes. Bar plots illustrating the enrichment of VCP protein, which has been reported to interact with UFD1L (also shown) and that was identified in the interactome. Sumo and UBE related proteins are also shown, which could be related to post-translational modifications of OCT4 recognised that could be recognised by UFD1. Proteins are shown for all conditions. LFQ (abundance) intensities were log2 transformed, centred and normalized.

Recognition by UFD1L of ubiquitinated OCT4 could be a regulatory mechanism for the degradation or relocation of OCT4 in chromatin, as it has been reported that recognition of ubiquitinated chromatin-associated proteins by UFD1L results in the remodelling and releasing of the ubiquitinated chromatin-bound substrate, which can be further degraded by proteasomes or recycled [288]. This evidence, and the fact that UFD1L levels in chromatin fractions of hES and O lin29-42 were lower (Fig. 4.12b), could suggest an

important mechanism for reprogramming in which the recognition of UFD1L of ubiquitinated proteins associated to chromatin, such as OCT4, results in their release from chromatin for degradation or recycling and relocation. Additionally, the higher levels of UFD1L observed in the chromatin fractions of OSKM 48h (Fig. 4.12b) suggest that this mechanism is induced by the OSKM expression. In fact, it has been shown that cMYC transcriptionally upregulates UFD1L in T-cell acute lymphoblastic leukaemia (T-ALL), as a mechanisms to alleviate the ER stress caused by accumulation of misfolded proteins [287]. Finally, UFD1L importance in reprogramming could also be linked to its involvement in clearing misfolded proteins. In fact early ER stress is an essential step for the reprogramming process and ectopic transient activation of the unfolding protein response increases reprogramming efficiency [291] which could explain the early UFD1L induction and activation from early stages or reprogramming.

4.4.1.3 XPO6

Exportin 6 (XPO6) is a G-actin nuclear export transporter that is specific for profiling-actin complexes [292]. Monomeric actin (G-actin) is the only directly recognized cargo of this protein so far, making XPO6 responsible for the regulation of nuclear actin levels. In addition, nuclear actin has been implicated in a variety of DNA-related processes including chromatin remodelling, transcription, replication, and DNA repair [293]. Interestingly, herein different actins were also identified to be associated with OCT4 either in OSKM 48h (WT and mutants) or in hESCs (Fig. 4.15).

Among the actins found in the interactomes were ACTL6A and ACTN1, which have been both associated with chromatin remodelling complexes such as SWI/SNF, INO80, SRCAP/SWR1 and the combined remodeller/histone acetyltransferase complex TIP60/NuA4 [294].

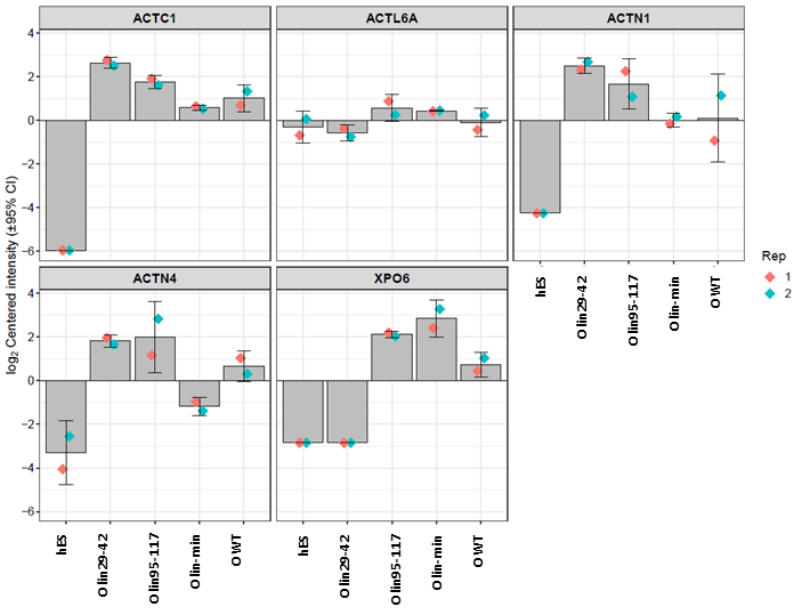


Fig. 4.15 Differential enrichment Actin proteins that were identified in the interactomes. Bar plots illustrating the enrichment of the actin proteins identified, which could be related to XPO6 (also shown). Proteins are shown for all conditions. LFQ (abundance) intensities were log2 transformed, centred and normalized.

Moreover, there is evidence suggesting that depending on the stimuli and cell conditions, the regulation levels of actin had different influences in transcriptional regulation. For example, mechanical strain conditions can result in the reduction of nuclear actin, leading to the attenuation of transcription and subsequent accumulation of H3K27me3 at facultative heterochromatin at differentiation genes. This effect can be reversed by depleting XPO6, which increased the levels of nuclear actin and the levels of H3K27me3 [295]. This example shows that depending on the cellular conditions, XPO6 is fundamental for regulating nuclear actin levels, which will determine global transcriptional activity. In reprogramming for instance, XPO6 KO had negative effects in iPS colonies formation, but interestingly its overexpression did not have any effects. This suggests that if the main role of XPO6 is to regulate actin levels, only the accumulation - not the absence or decrease levels- of actin in the nuclei are detrimental for the reprogramming process. Moreover, additional roles of XPO6 in chromatin independent of OCT4 should also be considered, as even if was not detected in O lin29-42 and hES interactomes, it was still detected in their chromatin fractions, with more enrichment in hES than in OSKM in general (Fig. 4.12b). Lastly, XPO6 could be involved in new transport

mechanisms, for example, XPO4 was reported to participate in a novel nuclear import pathway for SOX family in mESC, expanding the roles of exportins besides their established function in nuclear export [296].

4.4.1.4 MCMBP

Mini-chromosome binding protein (MCMBP) is involved in the regulation of the minichromosome maintenance complex (MCM), known to be crucial in the DNA replication process [297]. The MCM complex is comprised of six subunits (MCM2/3/4/5/6.7), each with a different role in the initiation and elongation of DNA replication [298]. They are involved in melting the origin DNA for the subsequent replication and fork progression, where the complex provides the DNA helicase activity necessary to unwind double stranded DNA during replication [299]. Studies in *Xenpous* egg extracts have demonstrated that the role of MCMBP in this process is to displace MCM2-MCM7 complex from the chromosomes after DNA synthesis is complete [300]. Furthermore, in human its downregulation results in increased apoptosis and abnormal nuclei exhibiting signs of replication stress and slowed cell cycle progression [301]. Thus, its importance in the cell cycle and DNA replication might explain the completely abolished reprogramming when the *Mcmbp* gene was deleted in MEFs (Fig. 4.9). In fact, MCMBP was al found as an essential gene needed for mESC maintenance and cancer cell survival [194, 302], suggesting a tight coordination of the cell cycle and reprogramming. Due to the important role of MCMBP for cell cycle progression [301], its chromatin-mediated association with OCT4 may directly link cell cycle regulation and reprogramming. Interestingly, OCT4 has already been associated in the regulation of cell cycle progression in embryonic stem cells by regulating the mitotic entry [303, 304]. More interestingly, it was also reported that the deletion of the N-terminal or C-terminal domain of OCT4 resulted in a significant impairments of the cell-cycle [305]. Other studies have also showed that alleviating the cell-cycle arrest induced by OSKM overexpression can increase the efficiency of reprogramming [306, 307]. As MCMBP is fundamental for the disassembling the MCM2-7 complex and the regulation of DNA replication, its chromatin association with OCT4 at early reprogramming could be part of a new mechanism implemented by the cells to cope with the cell cycle changes that OSKM are inducing. Besides, its absence in the hES and O lin-29-42 interactomes could

suggest this mechanism might be more necessary for the reprogramming process than for the pluripotency maintenance. However, the overexpression of MCMBP also has negative effects on reprogramming, suggesting a tightly controlled process is involved (Fig. 4.9 and 4.11).

4.4.1.5 RAI1

Retinoic Acid Induced protein 1 (RAI1) is a transcription factor that has associated to several human developmental disorders, including Smith–Magenis (SMS) and Potocki–Lupski syndromes, as well as other adult neural disorders with developmental origins such as schizophrenia and autism [308, 309]. Downregulation of RAI1 in cell lines derived from SMS patients showed dysregulation of genes that are involved with cellular growth and gene expression, while cells showed decreased cellular proliferation and longer population doubling [310]. These studies suggest a functional role of RAI1 in the transcriptional regulation, which may explain the decreased reprogramming efficiency observed in this work when RAI1 was KO (Fig. 4.9). In fact, other studies have linked RAI1 to transcriptional regulation as it contains two predicted protein-interacting domains: an extended plant homeo-domain (ePHD) and a nucleosome-binding domain (NBD) [311]. While RAI1 does not possess a known DNA binding domain, several studies have found its ability to bind nucleosomes [312] and have transactivation activity; its presence in both the nucleoplasmic and chromatin fractions [313]; and its binding to enhancers [314, 315] and specific loci in the genome, with strong enrichment around transcriptional start sites (TSS) and enhancer regions of genes involved in cell adhesion, axon guidance, and neuronal morphogenesis [313]. This evidence supports the association of RAI1 in chromatin and suggests that RAI1 association with OCT4 might be involved in transcriptional regulation mechanisms early reprogramming. Nevertheless, OCT4 is preferentially enriched at distal silent enhancers prior gene reactivation, recruiting RAI1 may enable promoter binding and gene activation [110]. Additionally, RAI1 promoter contains multiple retinoic acid responses elements (RARE), which can be recognized by the retinoic acid (RAR) and retinoid X receptors (RXR) modulated transcription factors [316]. Interestingly, one of these receptors (RXRA) was identified as an OCT4 chromatin associated protein in OSKM 48h (WT and mutants) but not in hES (Fig. 4.16). Moreover, even though RXRA was also identified in O lin29-42, its levels were less when compared

to the rest, particularly O lin-min and O lin95-117, which correlates with the levels detected for RAI1 in the corresponding interactome (Fig 4.16). Overall, RAI1 association with OCT4 does not only propose new transcription factors involved in reprogramming but could also illustrate how OCT4 might promote the expression of its interactors.

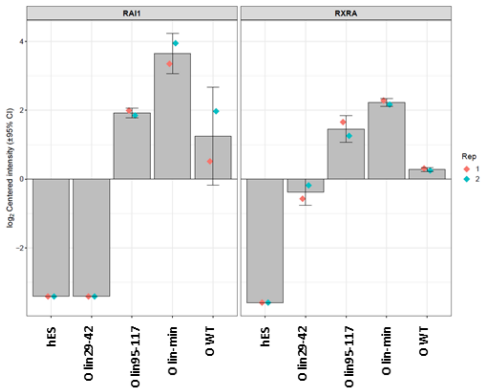


Fig. 4.16 Differential enrichment of retinoic acid related proteins that were identified in the interactomes. Bar plots illustrating the enrichment of the RXRA, which could be regulating the expression of RAI1 (also shown). Proteins are shown for all conditions. LFQ (abundance) intensities were log2 transformed, centred and normalized.

4.4.1.6 ETV4

E26 transformation-specific (ETS) transcription factor 4 (ETV4) is a transcriptional activator that has been described as an important factor in tissue development, such as motor neurons, mammary glands, kidney and limbs. Additionally, ETV4 has been described as an oncogene promoting proliferation and metastasis in colon, breast and prostate cancer, amongst others [317]. Amongst all the candidates proposed to be important for reprogramming in this work, ETV4 was the only one that enhanced reprogramming process when overexpressed along OSKM (Fig. 4.9 and 4.11). Similarly, ETV5 another member of the ETS family has already been reported to be important for the reprogramming process, as it has been defined as an early regulator and maker for reprogramming, necessary to generate poised intermediates with better chances of IPs cell formation [318], which agrees with the phenotype observed in the ETV5 KO reported in this work (Fig 4.11). Additionally, ETV5 can enhance reprogramming by facilitating the mesenchymal to epithelial transition (MET)[279]. In spite of ETV4 not been analysed in these contexts yet, it has been widely studied in cancer as it is overexpressed in several types, such as breast, prostate, colon and lung, besides being linked to metastasis and

cell proliferation [226]. Interestingly, in a human embryonic carcinoma (EC) cell line, ETV4 can act as an upstream effector to regulate the expression of the pluripotency core transcription factors OCT4 and NANOG by binding to its promoters. This supports the idea that ETV4 is involved in tumorigenesis as an oncogenic activator [317, 319] and suggests that ETV4, as a transcription factor, might be part of the mechanisms, along with OCT4, that re-activates genes involved in the pluripotency network in the reprogramming process. Indeed, an intermediate reprogramming populations with higher expression of ETV5 the early expression of this transcription factors, preceding the activation of the majority of transcription factors thought to be predictive for pluripotency induction [318], opening the question if by similar mechanisms ETV4 could be contributing to these transcriptional changes, therefore its contribution to enhance of the process (Fig. 4.11).

4.4.1.7 FBRSL1

FBSRL1 (Fibrosin Like protein 1) is the least characterized protein from the candidates. It belongs to the AUTS2 family, along with its paralogs AUTS2 and Probable fibrosis (FBRS), and has been associated to zebrafish development [320]. Even though FBRSL1 specific function remains elusive, AUTS2 studies in neurodevelopment suggest a role FBSRL1 in activating gene transcription via the Polycomb Repressive Complex 1 (PRC1) [321]. This evidence is supported by the fact that AUTS2, FBRS and FBRSL1 are co-binders of two specific subtypes of the PCR1 complex, termed PCR1.3 and PRC1.5 as they include the Polycomb group RING fingers PCGR3 and PCGR5 respectively [322]. Even though the canonical role of PRC1 complexes are involved in gene repression through the mono ubiquitination of H2AK119 through its RING1B component [323], the specific PRC1.5-AUTS2 is involved in activating transcription of neurodevelopmental genes [321]. The mechanisms mediating this unexpected role require the neutralizing of PRC1 repressive activity by the recruitment of the serine kinase CK2, which phosphorylates RING1B and compromising its mono ubiquitination activity [321]. Additionally, AUTS2 also recruits the histone acetyltransferase EP300 and the WD40-repeats containing protein WDR68, leading to gene activation of neurodevelopmental genes [322]. Interestingly, FBRSL1 was identified to bind AUTS2 complex [321] and even though AUTS2 was not present in the final list of proteins analysed in this work, the remaining principal components of the

PRC1 complex [324] were identified in the OSKM 48h interactomes, being fully identified in O lin95-117 and O lin-min (Fig 4.17).

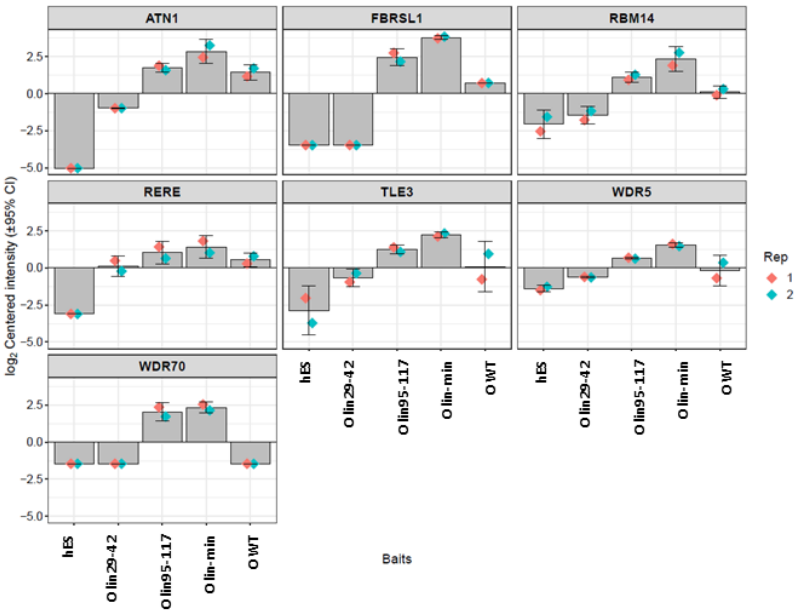


Fig. 4.17 Differential enrichment of proteins part of the PRC1.5-AUTS2 that were identified in the interactomes. Bar plots illustrating the enrichment of proteins that had been describe as part of the PRC1.5-AUTS2 complex and could be interactors of FBRSL1 (Also shown). Proteins are shown for all conditions. LFQ (abundance) intensities were log2 transformed, centred and normalized.

Moreover, proteins without a described role in the PRC1.5-AUTS2 but that were described to bind AUTS2 were also identified in the OSKM 48h interactomes, such as RERE, WDR5, TLE3, ATN1 and RBM14 (Fig. 4.18) [321]. Altogether, this suggests that in the early reprogramming, FBSRL1 might be involved in transcription activation via its interaction with the specific PRC1.3/5 complex and via the same mechanisms, its paralog AUTS2 is regulating transcription activation in neurodevelopment. More interesting is the addition of OCT4 to this mechanism and whether it is responsible of recruiting the complex to the chromatin or it is recruited once the complex is formed. Either way, the recruitment could be via its co-occurrence with the co-activator EP300, which is recruited to promoters by OCT4, SOX2 and NANOG in hES cells [151, 325, 326]. Additionally, PCGF5 and WDR68, which are main components of the PRC1.5-AUTS2 are dispensable in mESC maintenance, as their depletion had no effect in mESC self-renewal [322, 327], suggesting that the formation of this specific complex is not necessary for pluripotency maintenance. This last statement agrees with what is proposed in this work of FBRSL1

being required to promote but not maintain pluripotency. Altogether, the proteins identified in this works allows proposing a new mechanism for transcriptional activation, mediated by OCT4 and FBSRL1 via a non-canonical PCR1 complex capable of transcription stimulation of essential genes. This model is further supported by the evidence of deficiency of MEFs to reprogram to iPSCs when FBSRL1 is depleted and its absence along the main PRC1 components in the interactome of the deficient OCT4 mutant.

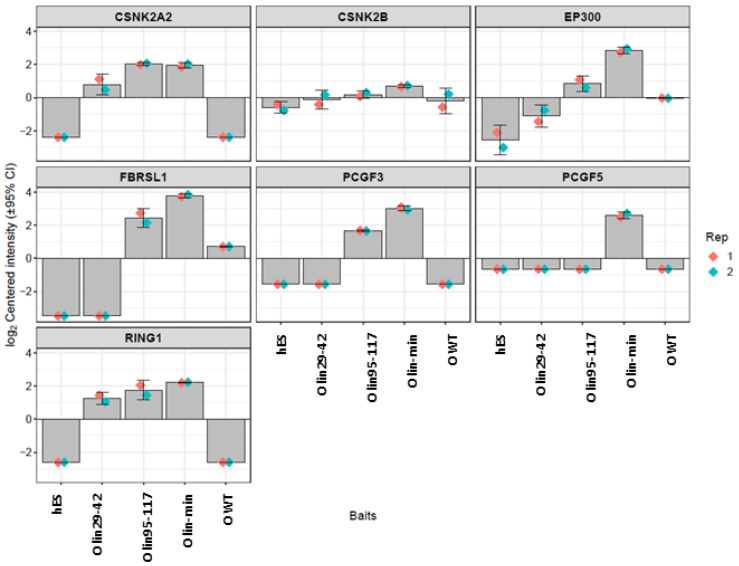


Fig. 4.18 Differential enrichment of proteins that interact with AUTS2 that were identified in the interactomes. Bar plots illustrating the enrichment of proteins that had been described as interactors of AUTS2 and could be interactors of FBRSL1 (also shown). Proteins are shown for all conditions. LFQ (abundance) intensities were log2 transformed, centred and normalized.

In summary, the evidence presented for each candidate represents new models that could be addressed to understand the importance of new candidate proteins in the reprogramming process as well as unravelling new mechanisms OCT4 is participating in to drive the process. Moreover, these proteins were identified as a result of the expansion of the OCT4 interactome at early reprogramming implementing ChIP-SICAP in mutants lacking essential and non-essential domains, revealing that focusing in the properties of the (TADs) of OCT4 can help understand new biochemical properties of OCT4, leading to the discovery of new interactors and mechanisms important for the reprogramming process and for the function of OCT4, information that could have not been addressed by taking the OCT4 interactome of pluripotent cells as the reference point.

Chapter 5 OCT4 DOMAINS INFLUENCE IN THE INITIAL ENGAGEMENT OF OCT4 WITH THE SOMATIC GENOME AND THE PROTEOME IN EARLY REPROGRAMMING

5.1 Introduction

Reprogramming initiation involves OCT4 acting as a pioneer factor by recognizing partial motif exposed in the surface of nucleosomes. This is followed by OCT4 opening up closed chromatin and recruiting other transcriptional activators and chromatin remodelers as well as the transcriptional machinery [110, 156]. An interesting feature of OCT4 and its adaptability to recognize partial motifs in nucleosomes relies on the flexibility of its DNA binding domain (DBD), being able to separately use each of the PouS and PouHD domains within the DBD (Fig. 1.3) [157]. Interestingly, targeting closed chromatin can occur by coordinate binding of OCT4 and the other reprogramming factors SOX2, KLF4, cMYC. In the two previous chapters (3 and 4), OCT4 was shown to be part of an early reprogramming proteomic network that differs from the pluripotency one. Importantly, analysis of different OCT4 mutants demonstrated that by deleting essential and non-essential domains can alter OCT4 protein interaction network on chromatin. Interestingly, these deletions are within the N- and C- terminal transactivation domains and not within OCT4 DBD, which makes direct contact with DNA. It is therefore unknown, how changing the protein interaction network of OCT4 can influence the engagement of OCT4 with the somatic genome during reprogramming.

Furthermore, the cellular localisation of OCT4 may also contribute to reprogramming beyond its transcriptional and pioneer function, which both take place in the nucleus. For example, it was shown that an OCT4 mutant that was actively exported from the nucleus was able to rescue self-renewal of OCT4-null ES cells, but had lower reprogramming capacity, in contrast with another OCT4 with a strong nuclear localisation, which had weaker reprogramming capacity [233]. This indicates that the nuclear as well as the cytoplasmic levels of OCT4 play a crucial role to maintain and induce pluripotency. Thus, defining the OCT4 protein partners in the cytoplasm during reprogramming may reveal new insights on OCT4 function in pluripotency.

5.2 Aims

- Define the initial engagement of the OCT4 mutants with the somatic genome in early reprogramming.
- Define direct protein-protein interactions of OCT4 on chromatin independent of DNA binding.
- Define OCT4 protein-protein interactions off-chromatin.

5.3 Results

The results and analysis of this chapter are presented in four main sections. First, OCT4 (WT and mutants) engagement with the somatic genome in early reprogramming was determined and analysed using ChIP-seq. Second, tagged-affinity purification was used to investigate the direct protein interaction of OCT4 WT and mutants on-chromatin in early reprogramming. Third, tagged-affinity purification was used to define OCT4 WT and mutants associated proteins off-chromatin in early reprogramming. Lastly, OCT4 WT and mutants nuclear distribution was analysed by confocal microscopy.

5.3.1 Deletions of non-essential domains enhance the initial engagement of OCT4 with the somatic genome

The proteomic analysis described in the previous chapters 3 and 4 showed that the deletion of various regions of OCT4 caused significant changes on the engagement with the chromatin-associated somatic proteome. To investigate if these deletions also changed the engagement of OCT4 with the somatic genome, ChIP-seq on OCT4 WT and mutants was carried out at the early stages of stages of reprogramming (OSKM 48h).

To define DNA enrichment of OCT4 in ChIP-seq, double cross-linking, sonication and chromatin immunoprecipitation were carried out as described for ChIP-SICAP (Section 2.X Materials and Methods). The DNA from three ChIPs for each condition were sequenced and aligned to the human genome. A model-based analysis for ChIP-seq (MACS) was used to identify genomic regions enriched for unique-mapped reads from ChIP-DNA over the input DNA (Fig. 5.1), identifying 499,788, 379,622, 266,473 and 159,002 enriched peaks for O lin-min, O lin95-117, O lin29-42 and O WT respectively. Binding of all OCT4 and mutants to genes that promote reprogramming, such as the mir-302/367 cluster [328]; genes necessary for mesenchymal-to-epithelial transition (MET), such as SNAI2 [329]; and apoptotic genes, such as TP53 [277], agreed with previous data

reporting the co-binding of OCT4 and the SKM factors to these set of genes at early reprogramming [110]; therefore, corroborating the peak calling results obtained. (Fig. 5.1d)[110].

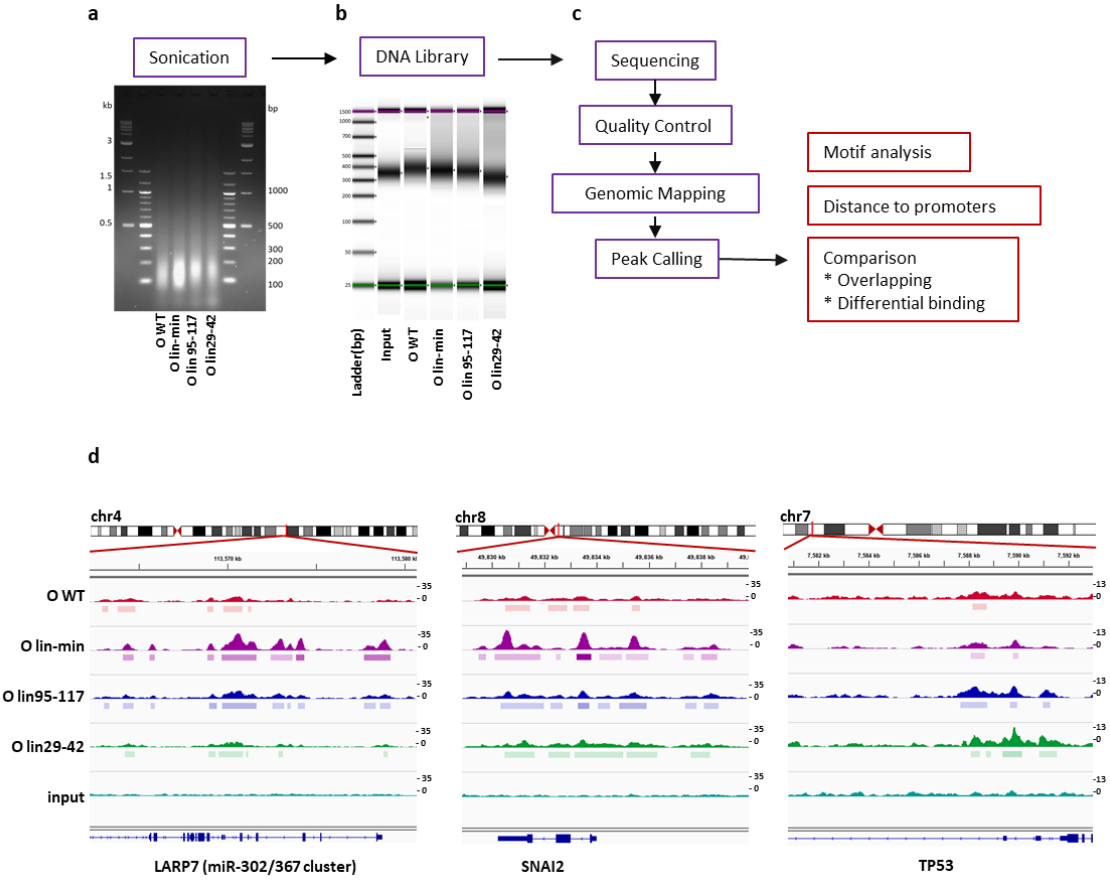


Fig. 5.1 ChIP-seq OSKM 48h Workflow. a. Sonicated DNA used for ChIP-seq analysis of OSKM 48h (WT and mutants). b. DNA libraries of the OCT4 ChIP sent for sequencing (WT and mutants). c. Workflow of the analysis applied to the ChIP-seq data. d. O WT, O lin-min, O lin95-117, O lin 29-42 and Input ChIP-seq profiles (red, purple, blue, green and aqua, respectively) at previously reported genes bound by OCT4 at 48h. OSKM peaks (bars) presented are normalized against input DNA sequenced tags (aqua).

To further investigate the similarities and differences between the binding patterns of OCT4 WT and mutants, peaks were grouped in shared and unique among the samples. To define common binding sites, peaks with an overlap of at least 50bp were considered resulting in a total of 81,866 peaks bound by all OCT4 WT and mutants (Figure 5.2)This represent a significant overlap with the occupancy of OCT4 WT (85% of WT peaks), indicating that the deletions within OCT4 mutants had minimal effect on targeting the

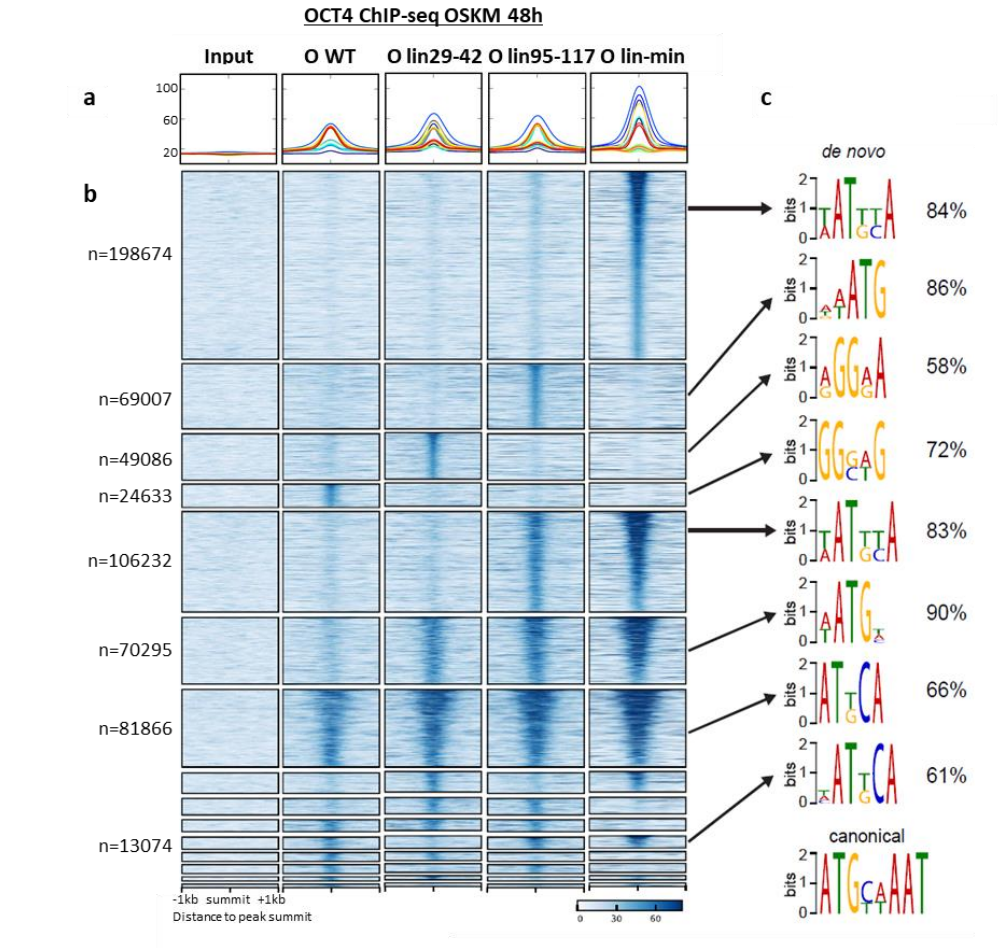
OCT4 WT binding sites (Fig. 5.2). Furthermore, the binding of OCT4 reprogramming-deficient mutant to these sites is not sufficient for generating iPSCs. Interestingly, the OCT4 mutants, especially those that can induce pluripotency, gained a large number of sites not targeted (n = 106,232) by O WTs (Fig. 5.2). Moreover, all OCT4 mutants as opposed to O WT gained a significant number of sites (n=70,295), suggesting that these new sites are not sufficient for OCT4 lin29-42 to drive reprogramming. Remarkably, O lin-min and O lin95-117 targeted far more sites suggesting that deleting the non-essential domains expand the engagement of OCT4 with the genome beyond the sites bound by O WT. This enhanced enrichment was particularly more significant with O lin-min (3 times more than O WT n=499,786), from which ~60% were unique (n=198,674) (Fig. 5.2). This suggests that deleting more non-essential domains further expand the engagement of OCT4 with the somatic genome. To address if the observed gain in binding sites of OCT4 mutants was mainly driven by low-affinity DNA binding, the intensity of OCT4 enrichment was measured and visualized in a read density heatmap (Fig. 5.2a-b). Interestingly, O lin-min was highly enriched at the new sites as well as those shared with OCT4 WT and other mutants, indicating high affinity binding (Figure 5.2a). This enhanced binding pattern is represented in specific genomic regions such as SMAD2 –which has been shown to improve reprogramming efficiency and kinetics [330] (Fig. 5.2c). Together these data suggest that deleting non-essential domains enhance the binding affinity of OCT4 to the somatic genome.

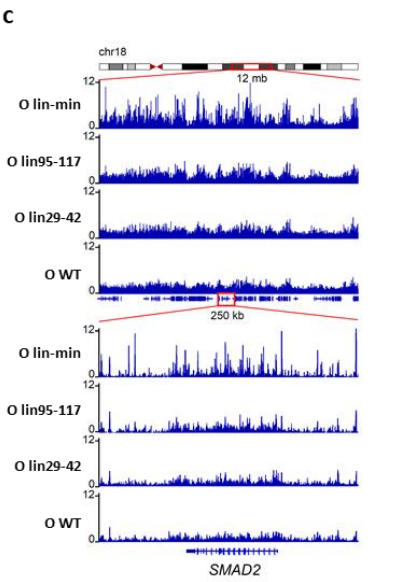
To further investigate whether the increase in binding sites was a result of unspecific binding, *de novo* motif analysis of the unique and shared peaks was performed. Sites shared by OCT4 WT and all the mutants were mainly enriched for partial OCT4 motif as previously reported [110] (Fig. 5.2c). Most importantly, the unique O lin-min sites were predominantly enriched for similar OCT4 motif, demonstrating that O lin-min targets specific new regions (Fig. 5.2c). Although, deletions of non-essential regions resulted in OCT4 uniquely targeting specific sites, deleting the essential regions resulted in OCT4 to uniquely target non-specific sites. Furthermore, sites that are unique to OCT4 WT were also predominantly enriched for non-specific sites. Thus, targeting more specific sites may explain why these mutants (lin-mini and lin95-117) were able to drive reprogramming compared to the deficient OCT4 mutant (lin29-42), which targeted more non-specific sites.

Lastly, the effects of deleting the non-essential and essential regions on the binding distribution of OCT4 relative the TSS was investigated using Genomic Regions Enrichment of Annotations Tool (GREAT). Interestingly, all shared and unique peaks showed a preference to bind TSS-distal sites (+/- 50 to 500 kb), similar to the overall distribution of OCT4 WT (Fig 5.2d). Moreover, the reprogramming deficient mutant O lin29-42 showed more binding TSS-proximal regions, which could be the result its non-specific and loosely bound profile. In general, these results are consistent with the TSS-distal distribution of OCT4 WT in early reprogramming; suggesting that promoter binding and transcriptional activation of target genes is a later event in reprogramming [110]. Therefore, deleting domains of OCT4 result in more engagement with the genome without changing affinity or specificity of OCT4 to target the distal element regions in early reprogramming.

5.3.2 Deletions of non-essential domains enhance the engagement of OCT4 with chromatin and its associated proteome

Altogether, the initial engagement of OCT4 WT and mutants with the genome correlates to the observed changes of the ChIP-SICAP results (See Fig. 4.4 and 4.5 in Chapter 4). The mutants, particularly O lin-min, also gained more chromatin-associated interactions when compared with O WT. Likewise, most of the O WT chromatin-binding partners were shared among the interactomes of the OCT4 mutants meaning that, as observed for the engagement with the genome, the new binding properties did not have an effect in the original O WT partners. In addition, O lin29-42 retained its capacity to bind to important chromatin-associated proteins as well as important genomic regions, indicating that although necessary, these are not enough for OCT4 to drive the reprogramming process. Moreover, the differences observed in the ChIP-seq analysis between O WT and the mutants' early engagement with the somatic genome, showed that deletion of non-essential domains confer OCT4 new properties that are not limited to their protein interactions, but also to their binding to the somatic genome at early reprogramming. Overall, ChIP-SICAP and ChIP-seq protocols were successful in pulling-down and isolating the different type of OCT4 mutants and their chromatin-association at the genome and proteome levels, revealing, for the first time, a significant increase in the number of proteins and genomic regions that associate with mutated versions of OCT4 in chromatin in early reprogramming to iPSCs.


OCT4 ChIP-seq OSKM 48h
Input
O WT
O lin29-42
O lin95-117
O lin-min
a
b
c
n=198674
n=69007
n=49086
n=24633
n=106232
n=70295
n=81866
n=13074
-1kb summit +1kb
Distance to peak summit
de novo
84%
86%
58%
72%
83%
90%
66%
61%
canonical
bits


c
chr18
12 mb
O lin-min
O lin95-117
O lin29-42
O WT
250 kb
SMAD2

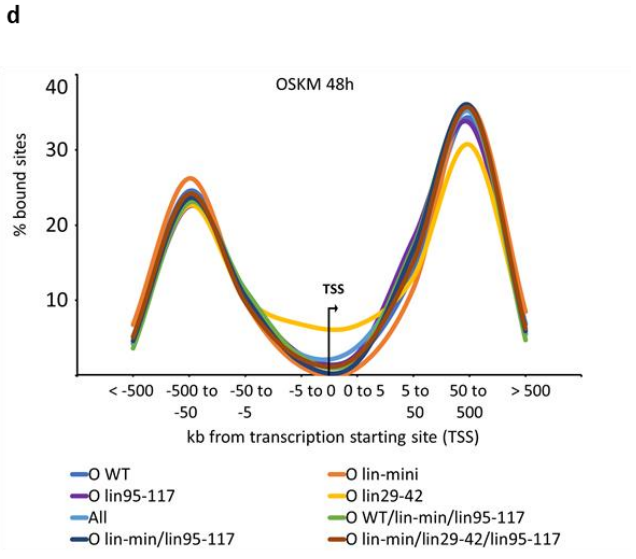

d
OSKM 48h
% bound sites
TSS
< -500
-500 to -50
-50 to -5
-5 to 0
0 to 5
5 to 50
50 to 500
> 500
kb from transcription starting site (TSS)
O WT
O lin-mini
O lin95-117
O lin29-42
All
O WT/lin-min/lin95-117
O lin-min/lin95-117
O lin-min/lin29-42/lin95-117

Fig. 5.2 Enriched engagement of OCT4 mutants with the somatic genome at early reprogramming. a. Peak profiles showing average read counts, which are input subtracted, lane-normalized, and as reads per million mapped reads. b. Read density heatmaps (in blue scale) showing the intensity of O WT, O lin29-42, O lin 95-117, O lin-min and Input signal (blue) spanning ±1 kb from the centre of the peak summit of the unique and shared peaks for each OCT4 (WT or mutant). The number of targeted sites is indicated for each combination, which corresponds to it in 5.2a. b. De novo sequence motifs overrepresented in the unique and shared peaks compared to the OCT4 canonical motif found in the JASPAR database. c. Binding profile of a genomic region including SMAD2 (zoom) that demonstrates the enhanced engagement with higher intensity of O lin-min when compared to O WT, O lin29-42 and O lin 95-117 d. O WT, O lin29-42, O lin 95-117, O lin-min O WT, O lin29-42, O lin 95-117 and O lin-min binding with respect to transcription starting site (TSS) display by the frequency of their unique and shared binding sites (all combinations).

5.3.3 Deletions of non-essential domains enhance the direct protein-protein interactions of OCT4 independent of DNA-binding

The correlation between the increase protein and genomic binding of the mutants compared with O WT suggests new properties conferred by the OCT4 deletions that could lead to new biological functions. The observed enhanced interactions with DNA and protein is not due to protein or chromatin levels, which are similar between all samples. However, this does not rule out the differences were influenced by the preferential antibody affinity for the cross-linked mutants over WT, which were used in the ChIP-SICAP and ChIP-seq methods. Therefore, ChIP-seq and ChIP-SICAP may yield better pull-down of protein and DNA interactors for OCT4 mutants than for WT.

To rule out this possibility, a FLAG-tag-affinity purification (FLAG-IP) using a different antibody and independent of cross-linking was implemented. This technique depends on a tag attached to the protein for its purification, using specific antibody for the tag instead of the antibody against the protein of interest. In this case a 3XFLAG was chosen and each OCT4 version (WT and mutants) was cloned in the dox-lentivirus system containing the 3XFLAG (3XF) peptide into the N-terminus (Fig. 5.5a). Additionally, the FLAG-IP was carried out from a non-cross-linked whole extract. This method will therefore identify proteins that directly interact with OCT4 in the nucleus due to the nuclease treatment, as well as proteins that interact with OCT4 in the cytoplasm. This is in contrast to ChIP-SICAP, which defines only chromatin associated OCT4 partners without distinguishing between the direct protein-protein interactions and those

mediated through chromatin and DNA. Nevertheless, comparing both protocols will allow defining the chromatin-associated proteins that can interact directly with OCT4.

Prior to the immunoprecipitation assays, protein levels and functionality of 3XF-O WT were tested to determine any negative effects of the tag. Proteins levels were tested by inducing 3XF-O WT and O WT in HF for 48h, followed by WB and Immunocytochemistry. The results are shown in Fig. 5.3, where both assays allowed the identification of WT and 3XF-O WT with similar levels as WT O, indicating that the tag does not affect the protein levels of the protein. In addition, difference in the molecular weight observed in the WB corroborated the 3XF tag in OCT4 (Fig 5.3b).

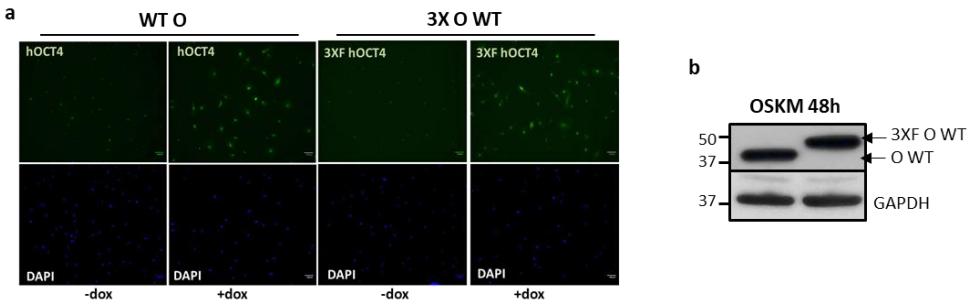


Fig. 5.3 3XFLAG does not affect the expression levels of O WT in OSKM 48h. a. Immunocytochemistry of WTO and 3XF O WT in OSKM 48h after dox induction. No dox induction is shown as a control. DAPI staining is shown to visualize the cells. b. OCT4 immunoblot detecting the tagged and not tagged (3XF) version of WT OCT4 in OSKM 48h after dox induction. GAPDH is shown as the loading control.

Next, 3XF-O WT was tested for its capacity to rescue the pluripotency maintenance phenotype in mESC to confirm the functionality of 3XF-O WT. To this end, a Pou5f1 KO mESC cell line used (ZHBTc4.1) containing a dox-off Pou5f1 transgene. These cells would therefore differentiate upon adding dox to the media unless a functional OCT4 is exogenously introduced to rescue the ability of these cells to self-renew (Fig. 5.4a) [271].

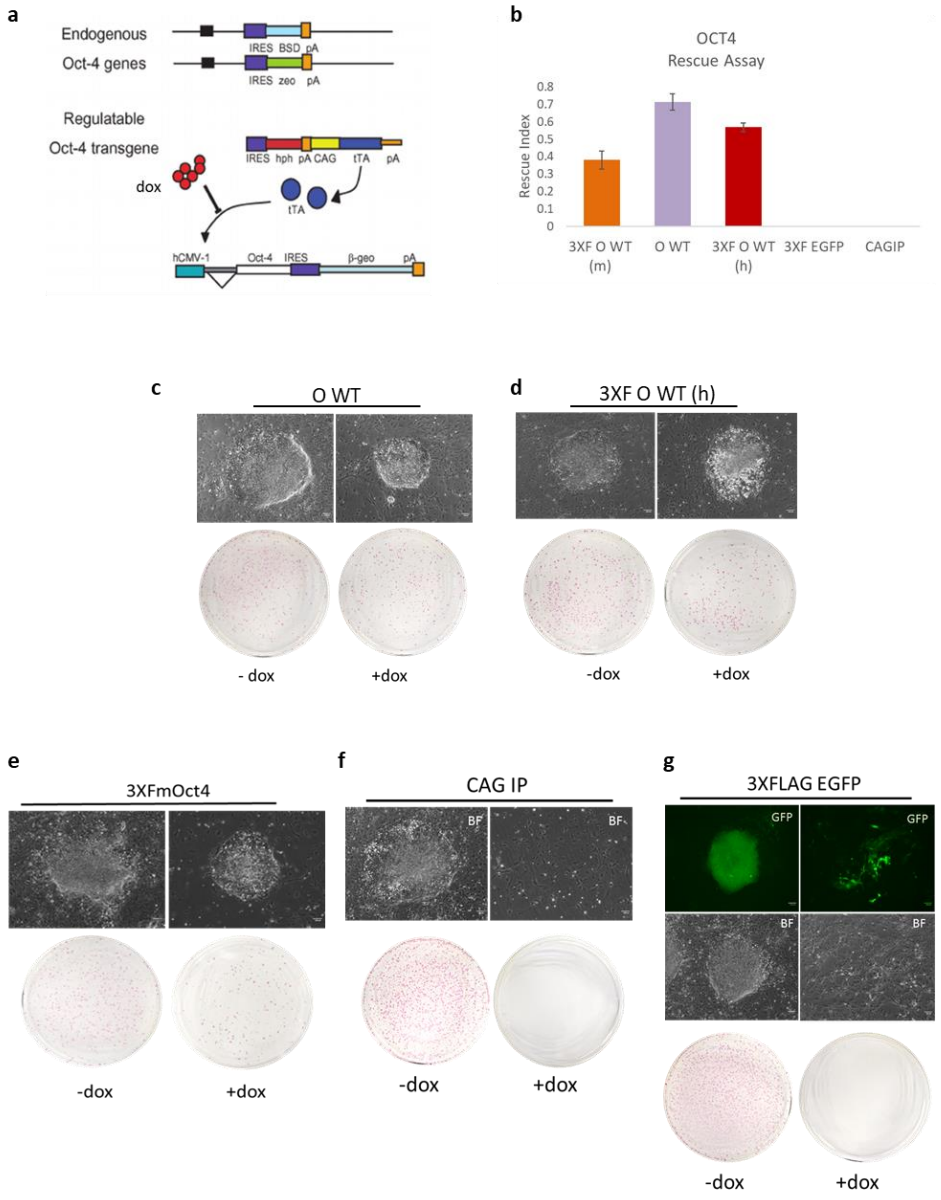


Fig. 5.4 Pluripotency and stem cell self-renewal rescue capacity of 3XF OCT4. a. Representation of the ZHBTC4.1 mouse cell line with the dox-regulatable Oct4 transgene. b. Pluripotency rescue index of WT O (tagged and untagged) after ZHBTC4.1 Oct4 transgene was repressed by dox. Rescue index was quantified by counting the number of AP stained mESC colonies +dox divided by colonies -dox. 3XFLAG WT O (mouse) is shown as a positive control. CAG-IP (empty vector) and 3XFLAG-EGFP are shown as negative controls. Average of three replicates are shown (error bars indicate ± s.d.). (c-g) Representative mESC colonies and AP stained dishes +/- dox of the rescue assays for O WT (c), 3XF O WT (d), 3XFmOCT4 (e), CAG-IP (f) and 3XF-EGFP (g).

The ability of 3XF-O WT to rescue the ZHBTc4.1 self-renewal was examined along O WT, 3XF-mOCT4 (mouse), 3XF-EGFP and an empty vector (CAG-IP) as controls. Alkaline phosphatase (AP) staining was used as a marker for pluripotency, allowing to define the rescue index as a ratio of AP positive colonies in the presence and absence of dox (Fig. 5.4c-g). This revealed that 3XFWT-O was able to rescue and prevent the differentiation process to almost similar levels to that of untagged OCT4-WT, indicating that the tag is not affecting OCT4 involvement in maintaining pluripotency and self-renewal in mESC (Fig 5.4b-g). Altogether, these results confirm the expression and functionality of 3XF-O WT.

After adding 3X FLAG tags to Oct4 WT and each of the other mutants (Fig. 5.5a), HF were transduced with dox-inducible lentiviruses of the tagged OCT4 derivatives each in combination with SKM, which were induced for 48 h (Fig. 5.5b). HF with no OSKM induction were used as controls. The IP was carried out from whole cell lysates using beads-conjugated Anti-FLAG antibody under native conditions to preserve protein-protein contacts. The enriched proteins were eluted by competition with a synthetic 3XFLAG-peptide, to reduce the antibody heavy and light chains in the purified fractions, which can dominate in the mass-spec identification of the eluted proteins. Five consecutive elutions were performed for each 3XFOSKM 48h (WT and mutants) in three replicates. WB analysis confirmed the presence of OCT4 in all the elutions of all 3XFOSKM 48h (WT and mutants) and no in the non-infected HF control (Fig. 5.5c), confirming the capture and elution 3XF OCT4. Additionally, total protein staining of the resolved eluted fractions in SDS-PAGE revealed a significant enrichment of proteins in comparison to non-infected HF (Fig. 5.5d). In summary, these results demonstrate the specific purification of each 3XFOCT4 in early reprogramming (3XFOSKM 48h) and a successful recovery of OCT4 and its binding proteins.

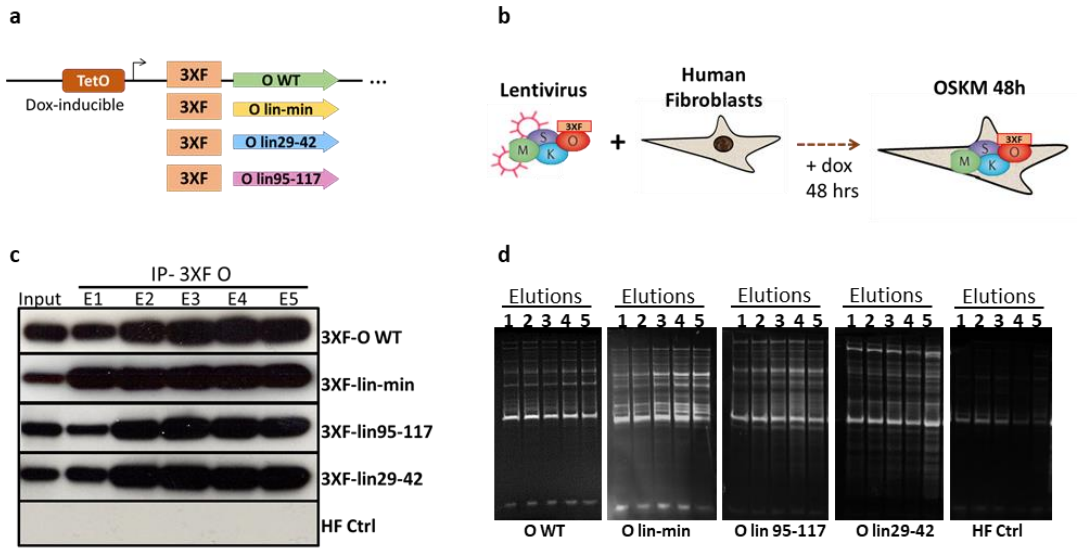


Fig. 5.5 3XFLAG-Affinity purification methodology to detect the protein binding profiles of tagged OCT4 (WT and mutants). a. Representation of the N-terminal 3XFLAG OCT4 (WT and mutants) constructs in a dox inducible lentivirus system. b. Workflow of (3XF) OSKM induction showing the transduction of HF with the lentiviruses, followed by the addition of dox and the induction of OSKM expression for 48h. c and d. 3XFLAG-OCT4 IP of total extract of OSKM 48 hours (WT and mutants). Proteins were eluted (E1-E5) by competition with a 3XFLAG Peptide and ran for OCT4 detection in a WB (c) and in a SDS-PAGE for SYPRO® Ruby staining of the eluted proteins.

For MS analysis three replicates were analysed for each condition (WT, mutants and control). For each replicate, the pooled five eluted fractions from each IP were run on a SDS-PAGE for-in-gel digestion followed by peptide purification using StageTips. The recovered peptides were processed by LC-MS and MaxQuant software was used for the identification of the corresponding proteins against the UniProt human database. Each interactome was filtered against the control and only considering proteins present in least two out of three replicates. A total number of 568, 1065, 719 and 840 proteins were identified for 3XF O WT, 3XF O lin-min, 3XF O lin95-117 and 3XF O lin29-42,respectively (Fig. 5.6). The bait OCT4 was identified among the top hits in all IP samples (Fig. 5.6) (Appendix Table 3). Cellular localization GO analysis of each 3XF-O interactomes (WT and mutant) in early reprogramming revealed a mixture of nuclear and cytoplasmic proteins, as the proteins were IPed from whole cell extracts without chromatin enrichment (Fig. 5.6). As observed in ChIP-SICAP, the OCT4 mutants, especially 3XF O lin-min, interacted with significantly more proteins than 3XF O WT. Thus, the differences observed in ChIP-

SICAP and IP were not due to cross-linking or antibody bias. Instead, they are indeed conferring OCT4 the capacity to interact with more proteins.

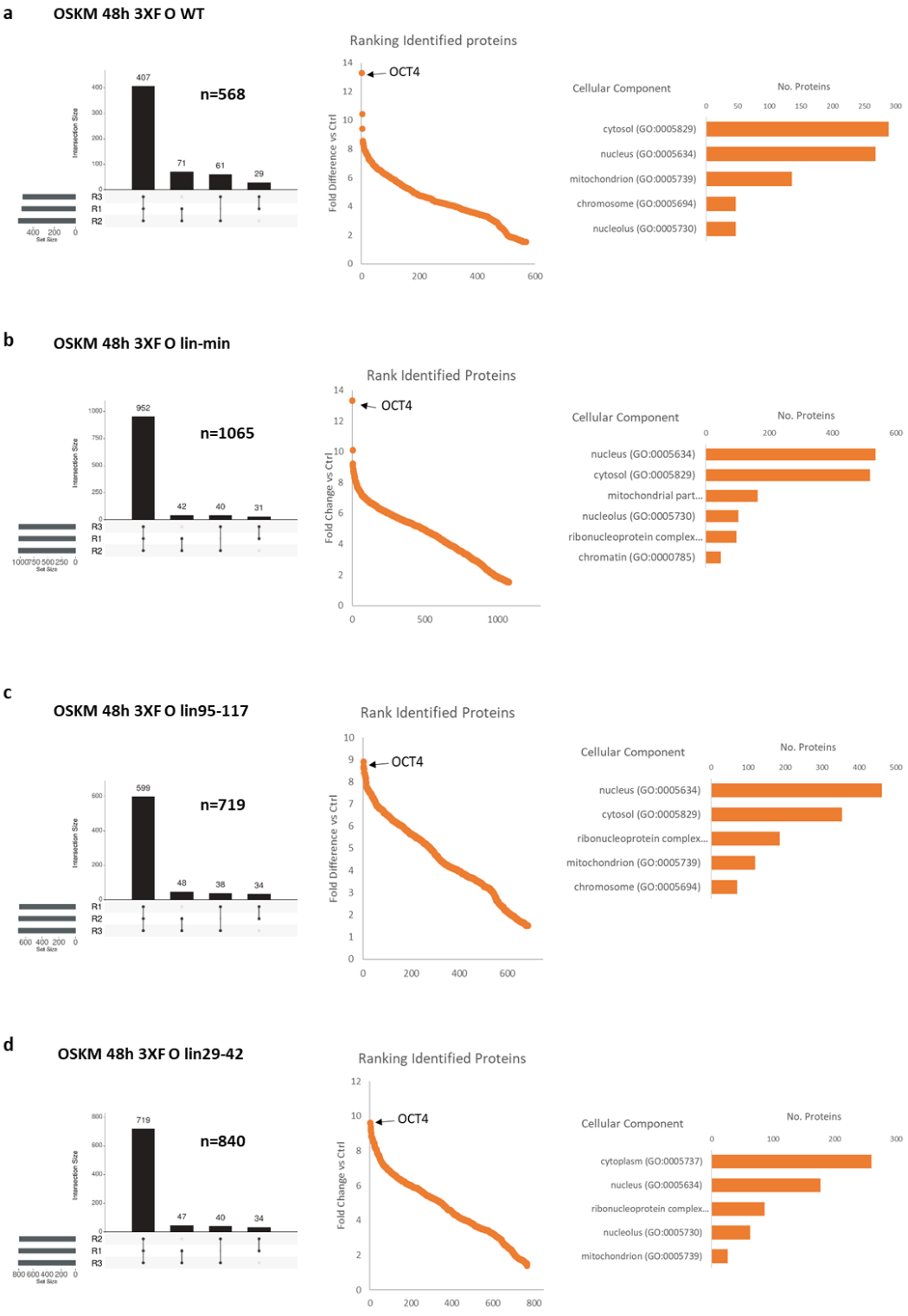


Fig. 5.6 FLAG-IP identified cytosolic and nuclear OCT4 interactors at early reprogramming. a-d. UpSet plot of each 3XFO interactome (WT and mutants) showing the intersection of identified proteins among the three replicates analysed by MS and filtered against the control. Ranking of the identified proteins and Gene Ontology enrichment analysis for Cellular component is shown for each OCT4: 3XF O WT (a), 3XF O lin-min (b), 3XF O lin95-117 (c) and 3XF O lin29-42 (d).

To define the proteins that directly interact with OCT4 on chromatin, the interactomes of ChIP-SICAP were compared to the FLAG-IP counterparts. The overlap of the FLAG-IP proteins was 15 to 20% of the total ChIP-SICAP interactome, being 59, 157, 161 and 216 shared proteins for O WT, O lin95-117, O lin29-42 and min respectively (Fig. 5.7).

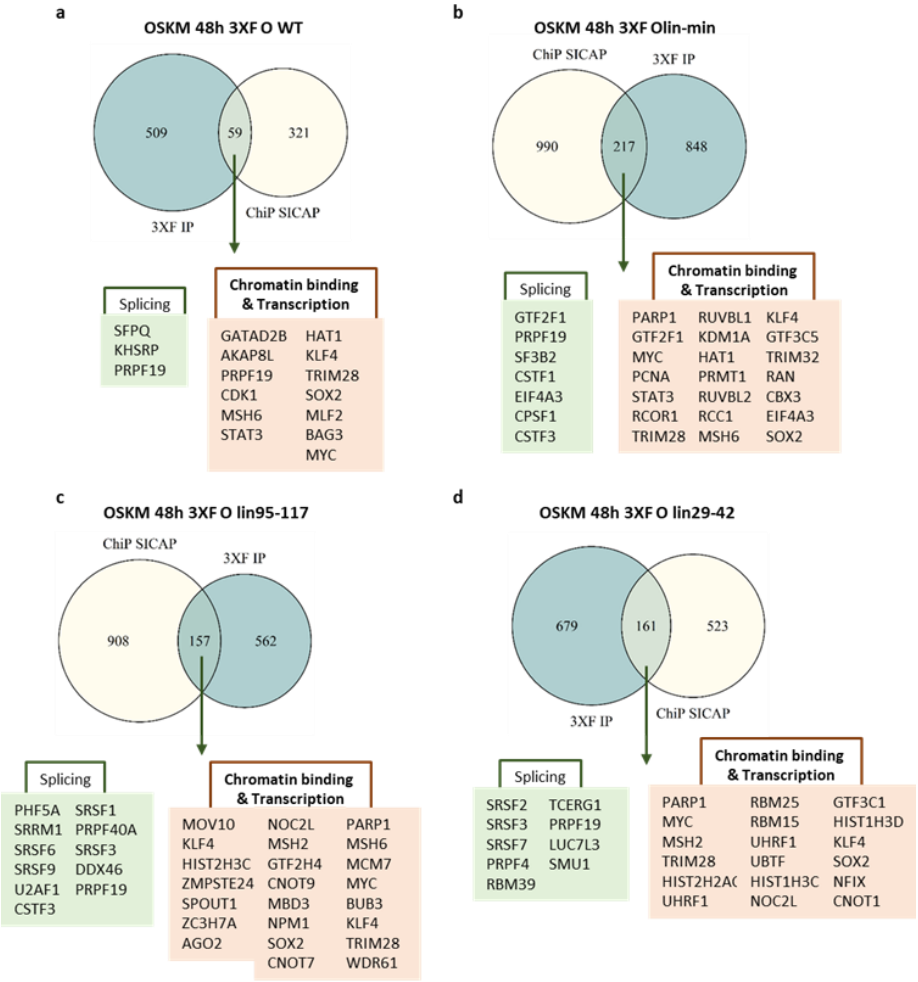


Fig. 5.7 Proteins identified in both proteomic approaches for OSKM 48h OCT4 (WT and mutants). Venn diagram of the overlapping interactors identified at OSKM 48h in both ChIP-SICAP (yellow) and FLAG-IP (blue) for 3XF O WT (a), 3XF O lin-min (b), 3XF lin95-117 (c) and 3XF O lin29-42 (d). Boxes represent shared proteins involved in splicing, chromatin binding and transcription.

This low overlap can be a result of the different purification conditions mentioned above, where FLAG-IP used the whole extract, identifying also cytoplasmic and the soluble nuclear (not-chromatin associated) proteins, unlike the chromatin-dependent interactions in the ChIP-SICAP protocol. Despite this, the percentage of overlap between ChIP-SICAP and FLAG-IP is proportional to the number of identified proteins for each OCT4 mutant. Additionally, the proteins identified by both methods for each OCT4 (WT and mutant) were involved in the processes enriched in the ChIP-SICAP analysis, such as gene transcription, splicing and chromatin binding (Fig 5.7 boxes). Altogether, the enhanced binding of OCT4 mutants in early reprogramming was not due to the technical particularities of ChIP-SICAP steps, as using different antibody and purification strategy still resulted in the identification of more protein interactors for the mutants. Most importantly, the proteins identified in both FLAG-IP and ChIP-SICAP confirmed a subset of interacting partners that can be defined as direct protein-protein interactors of OCT4 on chromatin, suggesting an important role of these proteins for the function of OCT4 in the chromatin context at early reprogramming. However, this does not rule out other proteins identified by ChIP-SICAP to also directly interact with OCT4 due to the limitation of FLAG-IP method.

5.3.4 Deletions of non-essential domains enhance the engagement of OCT4 with the cytoplasmic proteome

An interesting observation of the FLAG-IP interactomes was the identification of non-chromatin associated proteins (nuclear and cytoplasmic) as OCT4 interactors in early reprogramming. This observation correlates with the presence of OCT4 in both the cytoplasmic and nuclear fraction in early reprogramming (WT and mutants)(see Fig. 4.12a, in Chapter 4), suggesting that the interactions of OCT4 with cytoplasmic proteins may play a crucial role during reprogramming.

To investigate the cytoplasmic or off-chromatin proteins detected as OCT4 interactors and how the deletions were influencing these interactions, the 3XF OCT4 interactomes were compared focusing on the off-chromatin associated proteins; therefore, the proteins identified in the ChIP-SICAP and 3XFLAG IP overlap for each interactome were removed. A final number of 509, 848, 562 and 679 proteins were analysed for 3XF-O WT, 3XF-O lin-min, 3XF-O lin95-117, 3XF-O lin29-42 respectively (Fig 5.7 blue circles).

Intersection analysis revealed the presence of a core interactome shared between all OCT4 variants and that 3XF Olin-min was the mutant with most unique interactors (Fig. 5.8), which is similar to that seen in ChIP-SICAP. Furthermore, even when the deficient mutant 3XF O lin-min is able to interact with the core protein network, these protein-protein interactions are not sufficient for reprogramming (Fig. 5.8). This is similar to what has been observed for the core protein network identified by ChIP-SICAP (see Fig 4.4d in Chapter 4). This general analysis revealed that the deletions are also influencing the interactions of OCT4 with off-chromatin proteins. Moreover, it supports the idea that O lin-min confers new properties that allows OCT4 to engage more with both proteins and DNA, as it was the variant with more unique off-chromatin interactors. This further correlates with its observed enhancement of chromatin-associated proteins observed in ChIP-SICAP and enhanced engagement with the somatic genome observed by ChIP-seq.

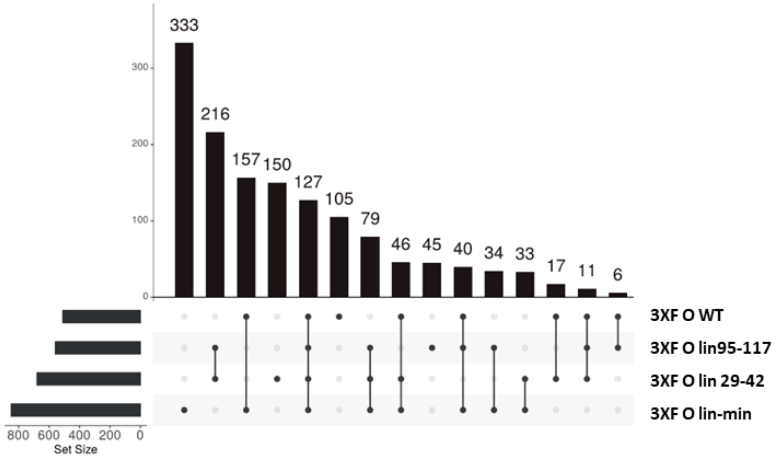


Fig. 5.8 Differential abundance of OCT4 off-chromatin-associated early reprogramming (WT and mutants). UpSet plot to represent the unique and shared off-chromatin binding proteins between interactomes of 3XF OCT4 (WT and mutants) in OSKM 48h.

Collectively, the new evidence obtained in this chapter from the 3XF-IPs revealed for the first time an OCT4 potential to bind to cytoplasmic proteins that might be relevant for the reprogramming process, suggesting its participation in molecular mechanisms independent of its canonical transcription/pioneer factor activity. Overall, these findings reveal the first non-nuclei biased interactome of OCT4, implicating that there could be new OCT4 protein interactions outside the nuclei that could be as relevant for a

successful reprogramming. Furthermore, it agrees with the statement that different domains of OCT4 confer different interacting properties.

5.3.5 Deletions of non-essential domains does not affect the ability of OCT4 to form nuclear puncta

Recent work has associated the transcription regulation activity of some transcription factors with their capacity to form phase-separated condensates with the co-activator Mediator complex MED1 [183, 331]. OCT4 alone is not able to form phase-separate condensates, but its intrinsically disordered regions (IDR) of its transactivation domains (TADS) (Fig. 5.9a) are responsible for the phase-separated condensates formed by MED1 in mESC super enhancers (SE), and can be observed as localized puncta in the nuclei at SE of key pluripotency genes [183]. Because the deletions of the mutants involved domains aligning with the low complexity regions of OCT4 (Fig 5.9a – arrows) and also enhancing both protein-protein and protein-DNA interactions, this opened the question whether this was due to promoting phase-transitioned protein condensation. In order to investigate the effects of the deletions in the formation of OCT4 puncta, OSKM 48h (WT and mutants) cells nuclei were visualized by high-resolution microscopy. The visualization by confocal imaging of OSKM 48h (WT and mutants) revealed no obvious differences in the formation of puncta in the nuclei between the mutants and WT OCT4 (Fig. 5.9b- blue boxes), and also showed puncta formation in the cytoplasm although at lower intensity (Fig. 5.9b-red boxes). These findings suggest that the deletions are not affecting the phase-transition protein condensation of OCT4, as mutants are still able to form puncta in the nuclei. Further co-localization of this puncta with co-activator complexes and nascent mRNA would help confirm these results, and could help understand more about the important regions of OCT4 transactivation domains in the formation of phase-separated condensates in the specific context of early reprogramming to iPSCs.

In summary, the results of this chapter corroborated that the different OCT4 domains influence not only the protein binding properties of OCT4 but also its interaction with the somatic genome in early reprogramming and demonstrated that by deleting non-essential and essential regions there is an enhancement in binding, especially when deleting two non-essential domains, as observed for O lin-min. Finally, the analysis of the off-chromatin interactome described for the first time the possibility of OCT4 being able

to interact with other proteins when localized in the cytoplasm, broadening OCT4 possible functions beyond and independently of its binding to DNA. These results open a new area of research to understand and optimize the reprogramming outcome when OCT4 is involved.

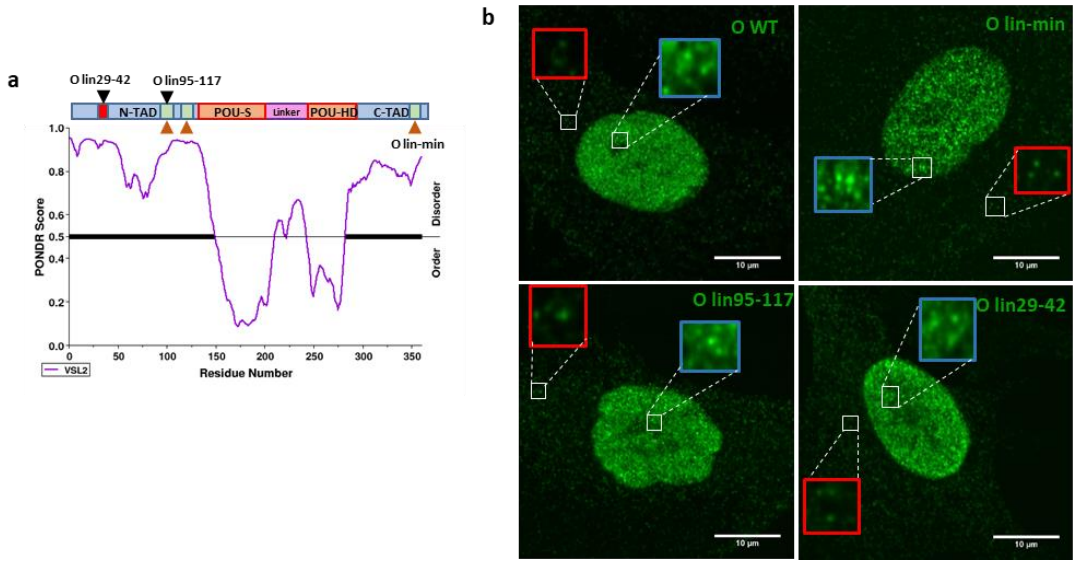


Fig. 5.9 OCT4 nuclear distribution at early stages of reprogramming (WT and mutants). a. Intrinsic disorder of OCT4 calculated by the VSL2 algorithm (pondr.com). Domains deleted in each region are denoted by arrows (O lin-min three deletions are denoted by the orange arrows) b. Representative confocal microscopy images of OCT4 IC (WT and mutants) and their nuclear puncta distribution in OSKM 48h. Blue and red boxes represent zooms of puncta in nuclei and cytoplasm, respectively. Scale bars = 10µm.

5.4 Discussion

5.4.1 Deletions of essential and non-essential domains enhance OCT4 engagement with the somatic genome

The identification of the chromatin-associated proteins of O WT and the mutants O lin-min, O lin29-42 and O lin95-117 (described in Chapter 4) confirmed that OCT4 not only differs in how it engages with the somatic proteome at early stages of reprogramming when compared with pluripotency, but it also uncovered that the deletion of essential and non-essential domains of OCT4 enhances its capacity to interact with more chromatin-associated proteins. Similar results were obtained in this chapter, when the initial engagement of WT and the mutants was compared by analysing their genome wide-binding profiles (ChIP-seq) at early reprogramming (Fig. 5.2). Most notably was how theses deletions expanded OCT4 capacity to recognize more sites beyond the original sites bound by O WT (Fig. 5.2), consistent with how the mutants can interact with more chromatin-associated proteins while preserving the interactions detected in O WT (See Fig. 4.4 in Chapter 4). Most importantly, the deletions of non-essential domains preserved the ability of OCT4 to target specific sites, which is in contrast to deleting the essential domains that caused OCT4 to target many non-specific binding sites. Moreover, these non-specific sites tend to be located closed to TSS, in contrast to the other new specific sites, which as those original sites, are predominantly distal to TSS [110]. This suggests that the deletion of non-specific domains but not the specific domains enable OCT4 to engage more genomic sites without altering the POU DNA binding motif (DBD) specificity In conclusion these findings highlight the functional contribution of these essential OCT4 domains in reprogramming not only by interacting with other proteins but also by targeting specific sites in the genome.

For instance, the deficient mutant O lin29-42 was still capable of binding the same sites as O WT, and most of its new binding sites were shared with O lin-min and O lin95-117 (Fig. 5.2). The same pattern was observed in ChIP-SICAP, where O lin29-42 chromatin-associated proteins were shared with WT O and the mutants (See Fig. 4.4 in Chapter 4). The interesting behaviour of this mutant revealed that although necessary, the interaction of OCT4 with those chromatin-associated proteins and genomic regions is not enough to drive the reprogramming process. In fact, the identification of a subset of proteins not associated with O lin29-42 allowed the description of new uncharacterised

important proteins for the reprogramming process. It is noteworthy that unique binding sites were also detected for O lin29-42 that had the particularity of being less specific and bind near promoters and the TSS. Therefore, approaches focusing in investigating both, the unique and missing sites of O lin29-42 could lead to new essential binding sites, as well as roadblocks non-previously described or associated with reprogramming.

ChIP-SICAP in Chapter 4 (See Fig. 4.3 and 4.4 Chapter) revealed that O lin-min was the mutant with more unique new proteins. The same was observed with ChIP-seq data, which revealed an increase of unique DNA binding sites, which were revealed to contain the OCT4 motif, discarding the possibility of them being unspecific. Besides, the analysis of the peak's intensity allowed to discard the possibility that the identified were the result of transient and loosely binding to DNA, suggesting that O lin-min is able to target more specific sites and with high affinity. Further structural studies could help understand how this mutant is able to engage more to DNA and proteins. One possibility could be that as a smaller size of the protein enables this OCT4 variant to easily access the genome. In addition, the deletion of non-essential regions may stabilize the formation of protein complexes on chromatin by eliminating the competition of other proteins that are usually associated with these domains. Nonetheless, it is still interesting that O lin-min does not enhance reprogramming efficiency; however, these deletions may enhance reprogramming kinetics, which has not been investigated.

Moreover, combining the results of ChIP-SICAP and ChIP-seq shows that the increase in DNA binding is associated with the increase of chromatin-associated proteins. This opens an interesting question of whether OCT4 mutants' abilities to interact with more proteins and more genomic sites are mutually inclusive. Nevertheless, the correlation of both ChIP-SICAP and ChIP-seq allowed the expansion of proteins and genomic regions that OCT4 is capable of interacting with at early reprogramming, while drawing special attention to the importance of the characterization of the transactivation domains of OCT4 for its engagement with both, proteins and DNA.

5.4.2 Deletions of essential and non-essential domains enhance OCT4 off-chromatin protein interactions

The evidence of the mutants' enhanced protein and DNA binding led to investigate if the differences observed were the result of methodology biases. By defining the interactomes of tagged (3XFLAG) versions of OCT4 (WT and mutants) and by implementing an affinity tag immunoprecipitation protocol (IP) at early reprogramming, it was evidenced that despite using different methodology, more interacting proteins were detected in the mutants (Fig. 5.5), proving that the method was not biasing the results. Moreover, the differences between ChIP-SICAP and IP allowed to expand the OCT4 interactome at early reprogramming and allowed to define OCT4 binding partners that were both, associated in chromatin and direct protein-protein interactors. Additionally, it allowed defining new off-chromatin protein interactions, both nuclear and cytoplasmic. Despite OCT4 findings that it can shuttle between the nucleus and the cytoplasm, few studies have been focused in studying its spatiotemporal dynamics and the idea that OCT4 may have functions in the cytoplasm has not been fully addressed. By analysing the off-chromatin interactors identified for WT O and the mutants, similar enhancement for 3XF O lin-min to bind more proteins was observed, agreeing with the ChIP-SICAP and ChIP-seq results.

Further literature-mining of some of the shared proteins present in 3XFO WT, 3XFO lin-min and 3XFO lin95-117 but absent in deficient 3XFO lin29-42 suggested that OCT4 partners could be linked to signalling pathways. As observed in the intersection graph in Fig. 5.9, a set of 40 proteins were shared between the reprogramming 3XFO WT, 3XFO lin-min and 3XF-O lin95-117 and not present in deficient 3XF-O lin29-42. Among these proteins, three elements of the TGF-beta Signalling Pathway were found: TAB1 (TGF-beta Activated Kinase 1 (MAP3K7) Binding Protein 1), phosphatase PPM1A (protein phosphatase, $Mg^{2+/}Mn^{2+}$ dependent 1A) and ITGA2 (integrin subunit alpha 2). Interestingly, this signalling pathway is relevant for development and for the pluripotency maintenance of human ES [44]. Other proteins identified associated to development were NEDD4 and PPP4C. NEDD4 is a ubiquitin-ligase and key regulator of FGFR1 endocytosis and signalling during neuronal differentiation and embryonic development [332], while PPP4C is a Protein phosphatase which was identified to be

required for ES self-renewal and pluripotency in a shRNA screen [333] and to be important for the regulation of the histone deacetylase 3 (HDAC3) activity [334]. Altogether, these proteins could indicate a role of OCT4 in signalling complexes, such as the reported complex of OCT4 with b-catenin and E-Cadherin in the membrane of ES cells [335]. Additionally, Heme Oxygenase 1 (HMOX1) was identified in the interactomes of 3XFO lin-min and 3XFO lin95-117. Interestingly, HMOX1, which is a cryoprotective factor, has already been linked to reprogramming. Human and mouse fibroblasts cells *Hmox1*$^{-/-}$ demonstrated decreased reprogramming efficiency in comparison to *Hmox1*$^{+/+}$ cells [336], endorsing the argument that other cytoplasmic non-chromatin OCT4 associated proteins are important for the reprogramming outcome. Therefore, the evidence presented in this chapter could open the field to understand the importance of OCT4 not only as a transcription factor bound to chromatin but also as a multifunctional protein during the reprogramming process. Further improvements to the protocol, such as protein identification of cell fractions could help corroborate the cytoplasmic function of OCT4 and lead to the identification of new important OCT4 interactors important for the reprogramming process in specific cellular localizations.

5.4.3 OCT4 could be involved in the formation of phase-separated condensates at early reprogramming

Phase separation is a physicochemical process by which molecules separate into a dense phase and a dilute phase. In cells, this process results in the formation of phase-separated bimolecular condensates, which include nuclear speckles, stress granules, nucleolus and transcriptional condensates, allowing the compartmentalization and concentration of biochemical reactions within the cells [331].

Involvement of OCT4 in phase-separated transcriptional condensates have been reported [183]. In mESC, OCT4 occupancy at enhancer elements is fundamental for the formation of mediator condensates at super enhancers of mESC. In this report, they also established that the amino acids of the transactivation domains (TAD) of OCT4 required for gene activation *in vivo* were the same required for the phase separation with Mediator condensates *in vitro*, proposing a model where the TADs of OCT4 confer the capacity to form phase-separated condensates with co-activators, in this case MED1, and regulate gene expression [183]. The particularity of OCT4, and other TFs, that allows the

formation of phase-separate condensates resides in the low-complexity amino acid sequence of its TADs, which are intrinsically disorder regions (IDRs) [183] (Fig. 5.11). As the essential and non-essential deletions of the OCT4 mutants involved domains residing in these IDRs, the capacity of the OCT4 mutants to phase separate with Mediator or other co-activators could be impaired or enhanced. One of the features to determine if OCT4 contributes to the Mediator condensates is to detect OCT4 puncta at the SE where MED1 puncta are also observed [183]. As a preliminary test to address the effects of these deletions on OCT4 capacity to contribute to phase-separation, the formation of OCT4 puncta was investigated revealing that all mutants were able to be part of nuclear as well as cytoplasmic puncta. However, as these analyses were mainly qualitative and not quantitative, differences between the mutants cannot be ruled out. These results indicate that the ability of OCT4 to assemble chromatin complexes that are functional in reprogramming can be uncoupled from its ability to drive phase-transitioned protein condensates and opens the field to investigate if the capacity of OCT4 to form phase-separated transcriptional condensates is a mechanism to regulate gene activation or chromatin remodelling in the reprogramming context.

Chapter 6 Thesis Overview and Perspectives

The research described in the previous chapters focused on exploiting proteomic approaches to identify the binding partners of the transcription factor OCT4, a main component of the pluripotency network and one of the original reprogramming factors. This was done in order to reveal the molecular basis by which OCT4 maintain pluripotency as well as induce pluripotency from differentiated cells. Studying both processes in the context of the human system will also expand our understanding beyond the well-characterized mouse system. Therefore, understanding the underlying mechanisms of human cellular reprogramming would help to improve the efficiency and the fidelity of the process, which is currently limiting its potential use for regenerative medicine. This final section highlights the main results and proposes further research based on this work.

6.1 Thesis Overview

6.1.1 OCT4 engagement with chromatin-associated proteins in hES revealed for the first time an OCT4 network in the human pluripotency context.

Taking into account the importance of the interaction of OCT4 with chromatin for the transcriptional regulation and the reshaping of the chromatin landscape, in Chapter 3 a proteomic approach that allows the identification of chromatin-associated proteins (ChIP-SICAP) was adapted to identify which of these OCT4 interacts with when bound to chromatin. Because of the lack of information about OCT4 in human embryonic stem cells (hES), the interactome of OCT4 in hES was described so it could serve two purposes: as a new resource to understand human pluripotency maintenance and as a more accurate dataset to compare and understand the differences of OCT4 involvement in pluripotency maintenance versus the reprogramming process in human. This was done successfully by identifying main proteins involved in the regulation of pluripotent stem cells. Among these proteins were components of pluripotency maintenance and transcriptional regulators previously reported to be important in both human and mouse, including SOX2, STAT3, LIN28a, SALL4, DNMT3A, DPPA4 and DNMT3B, as well as members of the chromatin remodelling complexes LARC, NURD and SWI/SNF. This set of transcription factors and chromatin regulators are constantly identified to be important for the pluripotency network and as part of mouse OCT4 interactomes, suggesting they

also play essential roles for the human pluripotency network and confirmed the involvement of OCT4 with the well stablished and conserved core pluripotency network in both, human and mouse. Moreover, beside the similarities found with previous work on mouse, the new dataset presented in this thesis allowed the identification of unique interactors for each species. It is noteworthy mentioning that the mouse dataset that was used for comparison was done in mESCs, which are in a naïve state of pluripotency, in contrast to the more primed state of hES; therefore, these differences could be involved in contributing to the naïve pluripotency state of mESC and the primed-like state of hESCs. Further characterization of this unique proteins and their importance could illustrate the different pathways that govern and differentiate human and mouse pluripotency, opening the research field to also analyse the OCT4 interactome of EpiSCs and investigate if it resembles more the one from hESCs, correlating with the more primed state of hES. For instance, besides the well stablished pluripotency associated proteins, the hES network included chromatin associated proteins which functions have not been described in either reprogramming or pluripotency maintenance. These group included histone acetyl-lysine readers, chromatin remodellers, transcription factors, histone modifiers, and proteins involved in mRNA processing, splicing and cell cycle associated, suggesting a potential role of these proteins along with OCT4 in chromatin structure, cell cycle and regulation of gene transcription and translation during pluripotency. Furthermore, once the importance of these proteins during pluripotency is established, they can provide insightful information of essential pathways and proteins that need to be activated to achieve the pluripotent state during human reprogramming, being potential candidates for a better understanding of human pluripotency and candidates to test in the reprogramming process.

6.1.2 OCT4 gains new chromatin-associated proteins at the early stages of human reprogramming

Having adapted the protocol for identifying chromatin-associated proteins and establishing the OCT4 interactome in hES, this work focused on studying OCT4 at an early stage of the reprogramming process, defined as 48hrs after the OCT4, SOX2, KLF4 and cMYC induction in human fibroblasts (OSKM 48h). Defining the chromatin-associated proteins of OCT4 at early reprogramming and comparing them against those of pluripotency, allowed the definition of a new OCT4 network specific for the early

reprogramming process that differ from the one in pluripotency maintenance. This evidence correlates with the differences observed in the initial engagement of OCT4 with the somatic genome when compared to hES. Taking advantage non-labelled quantitative proteomics the abundance of each identified protein was quantified, allowing the definition of four groups when the hES and early reprogramming (OSKM 48h) OCT4 were compared. These four groups were: unique in hES, shared with an enrichment in hES, shared with an enrichment in OKSM 48h and unique in OSKM 48h. Unique and enriched proteins in hES were enriched with proteins involved in pluripotency, supporting the role of this proteins for the maintenance of stem cells. Moreover, their enriched or exclusive interaction with OCT4 in hES and not early reprogramming indicates that their interaction with OCT4 occurs in the later stages of reprogramming, when most these proteins start to get expressed.

Of much interest was the group of proteins that were unique in OSKM 48h. This network was enriched for chromatin-modifiers and proteins involved in development and differentiation. Some of these proteins had already been reported to be facilitators or blockers of the reprogramming process, but most of them had no previous association with the process nor their interaction with OCT4. Enrichment of this group revealed a lesser amount of proteins involved in pluripotency maintenance and more proteins involved in differentiation and developmental processes, as well as chromatin structure, transcription regulation and lineage specificity. This suggests that proteins involved in differentiation pathways can contribute to the reprogramming through their association with OCT4 and suggest common mechanisms for cell differentiation and reacquisition of pluripotency, with OCT4 as an important component. A set of worth noticing proteins found in this group, are somatic specific transcription factors that have been reported to be downregulated in mouse reprogramming, such as HOXC10, RUNX1, FOSL1 and TAGLN. The downregulation of these somatic transcription factors is believed to contribute to the downregulation of the somatic genes at early reprogramming. How the OSKM regulate the repression of these specific genes is not yet fully understood, but evidence suggests that at 48hrs of OSK induction in MEFs, the OSK factors share binding sites with RUNX1 and FOSL1, thus detection of these proteins as OCT4 chromatin-associated proteins supports the evidence that they can co-bind in the genome at early stages contributing to the repression of somatic enhancers. Alternatively, these new somatic

TF-OCT4 interactions do not rule out the possibility of a synergistic function in which, before their downregulation, the somatic TF take part of transient complexes important for reprogramming, even if they are active in a short timeframe.

Most interestingly, an important set of the unique proteins OSKM 48h included proteins that have not been linked with OCT4 nor described in the reprogramming process, highlighting that the existing barrier in the understanding of OCT4 roles in reprogramming. For instance, the most abundant proteins identified in were two members of the Nuclear Factor I family, NFOC and NFIX. These proteins are site-specific DNA binding proteins that can promote the transcriptional activation or repression, depending on the cellular context; also they have been described as key epigenetic regulators and chromatin remodellers during development and cancer, opening the possibility of a new non-described OCT4/NFIC/NFIX complex involved in chromatin remodelling and transcriptional regulation at early stages of the reprogramming.

Altogether, the description of OCT4 at early reprogramming, proved that OCT4 not only interacts with chromatin-modifiers to reshape the landscape of the somatic genome, but also interacts with a new set of proteins, involved in development, lineage specificity, mRNA binding and differentiation. This evidence could link common mechanisms between these processes and the reacquisition of pluripotency during reprogramming, with OCT4 as an important central component.

Summing up, the comparison of chromatin-associated proteins between pluripotency maintenance and early reprogramming illustrated how OCT4 is a multifaceted factor that is able to change its chromatin-binding dynamics in order to adapt its functional interactors for the establishment of different phenotypes.

6.1.3 Essential OCT4 reprogramming domains are needed for the interaction of OCT4 with chromatin-associated proteins important for successful reprogramming to iPSCs

The identification of new OCT4 chromatin-associated proteins in early reprogramming led to investigate which of these proteins were functionally relevant and important for the reprogramming process. To elucidate some of these proteins, OCT4 mutants bearing deletions in its transactivation domains (TAD) were analysed. These OCT4 mutants were designed in a parallel research project developed in our laboratory focused in the

dissection of the OCT4 domains that are essential for reprogramming to iPSCs but not essential for pluripotency maintenance. Based on this analysis, essential and non-essential regions of OCT4 for reprogramming were defined and different OCT4 mutants were designed. ChIP-SICAP was applied to three of these mutants bearing different deletions in the transactivation domains (TADs); including two OCT4 mutants with reprogramming-capacity (Olin-min and O lin95-117) and one OCT4 mutant that is reprogramming deficient (O lin29-45). Comparison between the previously described networks of OCT4 WT in pluripotency and early reprogramming against the networks of the mutants was performed, with the hypothesis that the deficient OCT4 mutant would be missing important interactors present in all reprogramming versions of OCT4 (WT and mutants). This statement was supported by the identification a set of missing interactors in the OCT4 deficient mutant that were not previously linked to reprogramming and that were also absent in the pluripotency network, suggesting their interaction with OCT4 is relevant in early stages of reprogramming but not for pluripotency maintenance as the deficient mutant is still functional for the pluripotency maintenance of mES. These partners consisted of seven new OCT4 chromatin-associated proteins: UFD1L, RAI1, TNIP2, ETV4, XPO6, FBRSL1, and MCMBP and showed to be important for the reprogramming process as their depletion had negative effects in reprogramming efficiency of mouse embryonic fibroblast. Despite the specific roles of these proteins during reprogramming was not addressed in this thesis, the biological processes where they have been involved are quite varied, including nuclear export, protein degradation, stress-response, signalling response, post-translational modifications recognition, transcriptional regulation, chromatin remodelling and cell cycle. Furthermore, analysis of the enrichment of these candidates in the chromatin fraction suggested their recruitment to chromatin at early reprogramming might be mediated or influenced by OCT4 essential domains. Thus, dissecting the functional domains of OCT4 not only contributed to the identification of new partners crucial for reprogramming but also highlighted the versatility of OCT4 to be involved in different biological processes, either functionally or by facilitating the chromatin-recruitment of functional proteins needed to achieve the pluripotent state.

6.1.4 Deletions of essential and non-essential domains enhance OCT4 binding properties

An interesting particular finding observed when analysing the interactomes of the OCT4 mutants was the increase of chromatin-associated proteins able to interact with the OCT4 mutants when compared to WT. Intrigued by the fact that alterations in the TADs of OCT4 enhanced its protein interactions, ChIP-seq of the mutants at early reprogramming was assessed, showing the same pattern: altering the OCT4 TADs enhances the initial engagement of OCT4 with the somatic genome. Moreover, a different proteomic approach focused in whole cell extract and direct protein-protein interactions (IP) was tested to discard any methodology bias in the protein identification. Results using the latter approach confirmed that deleting essential and non-essential domains of the transactivation domains of OCT4 provides better genomic and proteomic engagement. Consequently, it allowed the identification of off-chromatin associated proteins, suggesting new OCT4 associations that do not depend on OCT4 being in interaction with the chromatin, and more interestingly, interactions that might occur in the cytoplasm. Remarkably, in all cases, the deletions of OCT4 non-essential domains resulted in higher protein and genomic engagement when compared with the deficient mutant bearing an essential domain deletion and WT. Interestingly, particularly for O lin-min, despite higher engagement with proteins and the somatic genome, its reprogramming efficiency was not improved, suggesting that the essential domains are important for more specific interactions with the genome and more functional interactions with the proteome that actually result in a more efficient reprogramming process. Overall, these results highlighted that not only the cellular process and environment impact OCT4 function, as deletion of essential and non-essential reprogramming domains expanded the engagement of OCT4 with both, the proteome and the genome, suggesting that different domains contribute to OCT4 binding profiles, providing an additional intramolecular diversity. Thus, characterizing of the TADs of OCT4 could help understand more about its biochemical properties while unravelling proteins and DNA binding sites that are important for the reprogramming process.

6.2 Perspectives

Since the breakthrough discovery that somatic cells can be reprogrammed to a pluripotent state in vitro to generate induced pluripotent stem cells (iPSCs), significant efforts have been made to increase the efficiency of this technique so it can be used in disease modelling, drug screening and regenerative medicine. When first described, the reprogramming process implied the addition of a defined cocktail of only four transcription factors, including OCT4, SOX2, KLF4 and cMYC (OSKM). Despite the simplicity from the technical perspective, the efficiency of reprogramming is quite low, especially in the human context, and the mechanisms underlying transcription factor-mediated reprogramming are still not fully understood. The work presented in this thesis tried to overcome some of these knowledge barriers by defining key molecular basis of OCT4 by exploiting proteomic approaches and describing for the first time its initial engagement with chromatin-associated proteins in early reprogramming and during pluripotency maintenance in embryonic stem cells. Moreover, it provided a novel proteomic dataset with interesting implications for the understanding of the different mechanisms involved in the human pluripotency maintenance and the early mechanisms involved in the somatic cell conversion to pluripotency. However, it should be noted that the data presented in this thesis represents a general and descriptive overview of OCT4 interacting proteins, which could not reflect functional importance in either process, pluripotency or reprogramming. Thus, further assays focused in the characterization of OCT4 interactors that are functionally relevant for reprogramming and pluripotency should be addressed.

The reprogramming of somatic cells to pluripotency requires the overexpression of not only OCT4 but also SOX2, KLF4 and cMYC, thus the expansion of the pluripotency network and the early reprogramming network by the application of the proteomic protocols described in this thesis will help provide a better insight into the mechanisms and the interactome dynamics involved in the pluripotency maintenance and the reprogramming of somatic cells to iPSCs. More importantly, expanding both the human pluripotency network and the early reprogramming network, can contribute to the identification of new proteins and molecular mechanisms involved in the reprogramming process that can be targeted with the final aim of improving the efficiency and fidelity of iPSCs generation.

Additionally, the identification of new proteins important for the through their chromatin-association with OCT4 at initial stages of reprogramming, has opened the field for their further characterisation, which could unravel the mechanisms they are involved in to promote pluripotency along with OCT4. First, their importance in human reprogramming should be assessed. Secondly, description of their engagement with the somatic genome at early reprogramming using ChIP-seq needs to be carried out. Such data will provide valuable information regarding the co-binding sites with OCT4. Furthermore, ChIP-SICAP could also be implemented in these proteins to find common chromatin-associated partners with OCT4 and expand the knowledge of the complexes they are involved in. Moreover, the list of candidates to test could be expanded by focusing in the unique proteins found in the interactome of the mutant O lin95-117. This mutant enhanced the reprogramming efficiency in mouse; therefore, some of its interacting proteins could be facilitators for the process. Not lastly, the unique proteins identified in the pluripotency network of hES could also be targeted because of their importance for the pluripotency maintenance, thus their overexpression along with the reprogramming factors could contribute for a better achievement of pluripotency during the reprogramming process.

As with the majority of studies, the design of the current study presents its own limitations that could be addressed in future research. For instance, the approach presented in this thesis focused in the initial stages of reprogramming without the isolation of particular cell intermediates, which gave the advantage of having enough starting material for the proteomic and ChIP-seq approaches. Thus, the application of these tools to study specific intermediate populations during later stages of the could be limited by the starting material, in addition of the need for a ChIP-grade antibody and by limitations in mass spectrometry to detect very low-abundance peptides. Therefore, ChIP and protein isolation techniques should be improved to maximize the amount of chromatin and protein purification, in addition to more sensitive mass spectrometry approaches. These improvements will be fundamental for future research to understand OCT4- and other TF- engagement dynamics with proteins and chromatin at different stages of the reprogramming process.

Lastly, the techniques and approaches described in this work could be expanded to gain a better understanding of transcriptional networks in general, and not only during pluripotency maintenance or during cellular reprogramming, as transcription factors are involved in multiple biological processes and diseases. Therefore, the integration of the identification of chromatin-associated proteins, off-chromatin associated proteins and genomic engagement of relevant transcription factors or chromatin-remodelling proteins could help extend and understand their function in physiological conditions and diseases in an integrated workflow.

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Appendix

Tables of identified proteins

Table 6.1 Identified proteins ChIP-SICAP

			LFQ Values ChIP-SICAP OCT4 (log2)									
Gene name	Uniprot	Pep	hES R1	hES R2	WT R1	WT R2	lin-min R1	lin-min R2	lin95-117 R1	lin95-117 R2	lin29-42 R1	lin29-42 R2
AAMP	Q13685	3	NAN	NAN	NAN	NAN	NAN	18.72	19.71	19.51	NAN	NAN
AASDHPPT	Q9NRN7	3	NAN	NAN	NAN	NAN	19.39	19.73	19.28	NAN	NAN	18.93
ACAA1	P09110	2	NAN	NAN	19.27	NAN	19.19	18.56	NAN	NAN	NAN	NAN
ACBD6	Q9BR61	6	NAN	NAN	NAN	21.86	22.13	21.20	NAN	21.27	22.02	21.53
ACP1	P24666	5	NAN	NAN	20.84	21.53	21.23	21.36	21.15	21.21	20.55	20.51
ACTC1	P68032	22	NAN	NAN	24.03	24.67	23.98	23.87	25.25	24.95	26.09	25.84
ACTL6A	O96019	14	22.11	22.85	22.36	23.02	23.21	23.24	23.67	23.04	22.41	22.04
ACTN1	P12814	36	NAN	NAN	20.71	22.78	21.49	21.80	23.89	22.72	23.96	24.31
ACTN4	O43707	42	19.29	20.79	24.37	23.65	22.38	21.96	24.50	26.17	25.30	25.01
ADNP	Q9H2P0	29	24.37	23.52	21.36	23.68	23.97	23.74	23.68	23.14	22.85	23.05
ADRM1	Q16186	4	NAN	NAN	NAN	NAN	18.61	18.60	NAN	18.82	18.92	NAN
AES	Q08117	7	NAN	20.36	21.17	22.09	23.47	23.67	22.42	22.14	NAN	20.97
AHCTF1	Q8WYP5	24	NAN	NAN	NAN	22.25	21.69	21.58	22.56	21.47	23.09	22.82
AHCY	P23526	10	NAN	NAN	NAN	NAN	21.26	21.43	21.88	22.57	21.42	21.71
AHDC1	Q5TGY3	41	19.63	19.94	20.54	22.29	26.01	26.36	23.86	23.75	19.32	20.60
AHNAK	Q09666	29	NAN	NAN	21.74	NAN	NAN	19.89	20.49	24.37	22.85	21.26
AHR	P35869	17	NAN	NAN	NAN	20.97	23.30	24.20	22.86	22.92	21.69	21.52
AHSA1	O95433	8	NAN	NAN	NAN	NAN	21.80	22.31	21.41	21.53	21.51	21.54
AIP	O00170	12	NAN	NAN	20.70	21.46	24.92	24.38	22.43	23.02	20.91	22.03
AK6	Q9Y3D8	5	NAN	NAN	NAN	NAN	21.46	21.49	NAN	NAN	NAN	NAN
AKAP8	O43823	12	NAN	22.01	NAN	NAN	22.36	22.03	21.99	21.14	21.48	21.39
AKAP8L	Q9ULX6	16	NAN	22.03	22.32	22.90	24.52	24.63	23.19	23.20	22.77	22.80
AKR1C1	Q04828	6	NAN	NAN	NAN	20.54	20.51	20.94	20.67	21.05	NAN	NAN
AKT2	P31751	7	NAN	NAN	NAN	NAN	20.33	19.89	19.81	20.16	NAN	NAN
ALDH18A1	P54886	33	24.58	25.32	NAN	NAN	25.96	25.84	20.65	22.78	25.58	25.40
ALDOA	P04075	17	21.78	NAN	22.72	20.53	21.04	21.33	22.22	25.02	22.92	21.96
ALKBH2	Q6NS38	7	NAN	NAN	NAN	NAN	21.74	21.98	NAN	21.03	NAN	NAN
ALKBH5	Q6P6C2	8	NAN	NAN	NAN	NAN	20.86	20.87	20.97	20.75	NAN	NAN
ALYREF	Q86V81	5	NAN	23.31	22.65	23.24	24.82	24.61	24.11	23.85	23.59	23.40
ANKRD54	Q6NXT1	6	NAN	NAN	NAN	NAN	21.61	21.65	21.09	21.04	NAN	NAN
ANP32A	P39687	8	NAN	22.55	21.14	22.12	22.21	22.32	23.10	22.79	22.73	22.55
ANP32B	Q92688	4	NAN	NAN	NAN	NAN	20.86	20.47	20.94	20.17	20.00	20.70
ANP32E	Q9BTT0	6	21.02	NAN	NAN	NAN	20.78	20.96	21.13	21.11	21.18	21.31
ANXA11	P50995	15	NAN	NAN	22.36	22.69	24.04	23.67	23.56	24.15	22.88	22.40
ANXA4	P09525	10	NAN	NAN	NAN	21.55	21.06	21.32	20.22	23.26	21.26	20.48
ANXA6	P08133	20	NAN	NAN	NAN	22.73	21.80	21.82	23.14	22.03	23.24	23.06
ANXA7	P20073	18	20.65	NAN	23.44	23.79	25.23	25.43	24.54	24.75	23.01	23.59
AP2A1	O95782	9	NAN	NAN	20.89	NAN	19.84	NAN	20.01	21.24	20.58	20.61
AP2B1	P63010	8	NAN	NAN	NAN	NAN	19.21	19.20	19.35	20.37	20.02	19.89
AP2S1	P53680	3	NAN	NAN	NAN	NAN	19.12	19.44	NAN	18.87	NAN	NAN
AP4B1	Q9Y6B7	11	NAN	NAN	NAN	NAN	21.13	21.01	NAN	NAN	NAN	NAN
APEX1	P27695	16	23.40	22.35	23.48	24.16	24.75	25.23	25.50	24.67	24.46	25.39
API5	Q9BZZ5	8	NAN	NAN	NAN	21.90	21.56	21.43	22.23	21.61	21.57	21.80
APOBEC3B	Q9UH17	4	NAN	NAN	NAN	NAN	19.08	19.41	NAN	NAN	NAN	NAN
APOD	P05090	6	NAN	NAN	NAN	NAN	19.03	18.58	NAN	19.59	19.58	19.84
APTX	Q7Z2E3	5	NAN	NAN	NAN	NAN	21.07	20.91	20.40	20.44	20.15	NAN
ARF4	P18085	7	NAN	NAN	NAN	NAN	22.78	22.56	23.10	23.28	23.73	23.45
ARHGAP23	Q9P227	3	NAN	NAN	NAN	NAN	17.39	18.33	NAN	NAN	NAN	NAN
ARHGAP39	Q9C0H5	2	NAN	NAN	NAN	NAN	18.01	17.94	NAN	NAN	NAN	NAN
ARID1A	O14497	49	24.52	22.73	20.43	21.93	25.21	25.16	24.67	24.12	20.72	20.85
ARID1B	Q8NFD5	37	21.88	NAN	20.08	22.18	24.64	24.94	22.51	22.38	19.55	19.86
ARID3A	Q99856	9	22.53	21.24	NAN	NAN	21.87	22.01	21.72	21.70	NAN	NAN
ARID3B	Q8IVW6	9	23.19	23.35	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
ARID5A	Q03989	3	NAN	NAN	NAN	NAN	18.91	18.82	NAN	18.77	NAN	NAN
ARID5B	Q14865	33	NAN	NAN	22.32	24.20	24.70	24.97	24.18	23.80	21.70	22.80
ARIH1	Q9Y4X5	5	NAN	NAN	NAN	NAN	20.36	20.17	20.18	20.41	NAN	20.96
ARIH2	O95376	8	NAN	NAN	NAN	NAN	20.38	20.55	20.08	20.16	NAN	NAN
ARMC7	Q9H6L4	2	NAN	NAN	NAN	NAN	18.12	19.23	NAN	17.65	NAN	NAN
ARNT	P27540	24	NAN	NAN	21.37	23.70	24.34	24.79	23.52	23.42	NAN	21.26
ARPC2	O15144	7	NAN	NAN	NAN	20.76	20.33	20.43	20.00	22.49	20.60	20.59
ARPC4	P59998	2	NAN	NAN	NAN	NAN	19.30	19.63	19.09	NAN	19.53	19.45
ASNS	P08243	3	NAN	NAN	NAN	NAN	19.02	19.13	19.28	18.99	NAN	18.99
ASPH	Q12797	2	NAN	NAN	NAN	NAN	NAN	NAN	19.13	NAN	20.41	20.06
ATF1	P18846	4	NAN	20.54	NAN	22.67	22.80	22.54	22.09	22.15	21.62	21.39
ATF7	P17544	3	NAN	NAN	NAN	NAN	20.34	20.40	19.37	19.51	NAN	NAN

ATN1	P54259	15	NAN	NAN	23.58	24.12	24.86	25.67	24.30	24.00	21.43	21.44
ATP2A2	P16615	5	NAN	NAN	NAN	NAN	NAN	NAN	NAN	20.62	20.12	19.68
ATP5B	P06576	12	NAN	NAN	NAN	NAN	17.91	18.06	NAN	24.09	NAN	NAN
ATP5F1A	P25705	11	NAN	NAN	21.52	NAN	20.71	21.06	20.24	23.06	20.75	20.76
ATP6V1A	P38606	10	NAN	NAN	NAN	NAN	NAN	NAN	17.34	22.63	17.66	NAN
ATRX	P46100	40	22.45	22.37	22.32	23.79	24.15	24.20	23.56	23.18	23.05	23.21
AURKA	O14965	9	NAN	NAN	NAN	21.21	22.00	21.62	21.70	21.41	NAN	NAN
AURKB	Q96GD4	12	22.91	22.55	21.34	22.27	21.88	22.09	22.36	22.26	21.33	NAN
AUTS2	Q8WXX7	10	NAN	NAN	NAN	22.76	22.87	22.43	21.81	21.89	NAN	NAN
BAG2	O95816	9	NAN	NAN	NAN	21.02	22.58	22.54	21.10	20.75	NAN	20.51
BAG3	O95817	19	NAN	NAN	22.29	23.34	23.57	23.25	22.55	22.80	22.64	22.41
BAG4	O95429	13	NAN	NAN	NAN	NAN	24.24	24.36	21.55	22.06	NAN	19.94
BAG5	Q9UL15	10	NAN	NAN	21.11	NAN	21.70	21.75	20.27	20.25	NAN	NAN
BAHCC1	Q9P281	6	NAN	NAN	NAN	NAN	19.48	19.83	NAN	NAN	NAN	NAN
BAHD1	Q8TBE0	9	NAN	NAN	20.97	21.03	21.46	21.53	20.82	20.94	NAN	19.92
BANF1	O75531	4	NAN	NAN	24.24	22.13	22.26	22.28	23.06	23.33	24.27	24.00
BAZ1A	Q9NRL2	21	NAN	NAN	21.60	22.01	20.87	20.86	22.36	20.89	NAN	20.58
BAZ1B	Q9UIG0	34	21.14	21.14	20.31	23.66	21.60	21.79	23.90	22.34	23.14	23.54
BAZ2A	Q9UIF9	16	NAN	NAN	NAN	NAN	21.83	21.88	20.93	19.78	20.36	NAN
BCAS2	O75934	4	NAN	NAN	NAN	NAN	20.05	20.31	21.63	20.87	20.84	21.56
BCCIP	Q9P287	6	NAN	NAN	NAN	NAN	19.97	19.56	19.96	19.51	NAN	19.50
BCL6	P41182	9	NAN	NAN	NAN	NAN	21.53	21.38	20.54	20.25	NAN	NAN
BCL9L	Q86UU0	22	NAN	NAN	23.65	23.95	23.92	23.59	23.97	24.09	22.05	22.51
BCLAF1	Q9NYF8	8	NAN	20.99	NAN	20.68	NAN	NAN	20.89	NAN	20.75	20.56
BCOR	Q6W2J9	52	NAN	NAN	22.31	23.81	25.02	25.12	24.44	24.18	20.82	22.69
BCORL1	Q5H9F3	5	NAN	NAN	NAN	NAN	19.59	19.86	NAN	NAN	NAN	19.45
BHLHB2	O14503	2	NAN	NAN	NAN	NAN	19.61	19.53	NAN	NAN	NAN	NAN
BLVRB	P30043	4	NAN	NAN	NAN	NAN	19.83	20.24	20.30	21.46	21.53	20.84
BNC1	Q01954	6	NAN	NAN	NAN	NAN	19.70	20.25	19.05	NAN	NAN	NAN
BOLA2	Q9H3K6	3	NAN	NAN	NAN	NAN	20.94	20.88	NAN	19.88	NAN	NAN
BRAT1	Q6PJG6	20	NAN	NAN	NAN	21.04	22.35	22.76	22.33	21.92	20.20	20.88
BRD2	P25440	15	NAN	NAN	20.78	22.09	22.32	22.28	22.87	21.75	20.06	21.17
BRD4	O60885	10	NAN	NAN	NAN	21.73	21.41	21.67	21.35	21.20	NAN	20.66
BRF2	Q9HAW0	4	NAN	NAN	NAN	NAN	20.46	20.19	NAN	19.07	NAN	NAN
BTAF1	O14981	27	NAN	NAN	NAN	21.55	22.22	21.92	23.45	22.89	22.25	22.10
BTBD14A	Q96BF6	9	NAN	NAN	22.56	21.16	21.62	21.21	20.85	20.71	NAN	20.82
BTBD14B	Q96RE7	17	24.10	23.25	24.62	24.80	25.84	25.96	25.33	25.04	24.30	24.48
BUB3	O43684	8	22.86	22.13	23.46	23.81	23.60	24.00	23.49	23.35	23.20	23.27
BUD23	O43709	6	NAN	NAN	20.85	21.57	22.26	21.90	21.11	20.99	NAN	21.37
BUD31	P41223	7	NAN	NAN	NAN	21.05	21.32	21.60	20.73	20.82	NAN	21.14
BYSL	Q13895	6	NAN	NAN	NAN	NAN	21.24	21.30	20.54	20.51	NAN	NAN
C15orf39	Q6ZRI6	27	NAN	NAN	20.51	20.29	23.93	25.25	22.90	22.68	NAN	20.75
C1orf174	Q8IYL3	2	NAN	NAN	NAN	NAN	18.57	18.95	NAN	NAN	NAN	18.80
C20orf27	Q9GZN8	3	NAN	NAN	NAN	NAN	19.38	19.44	NAN	NAN	NAN	NAN
C3orf38	Q5JPI3	13	NAN	NAN	20.79	21.42	24.25	24.08	22.35	22.24	NAN	21.67
C7orf26	Q96N11	8	NAN	NAN	NAN	NAN	21.95	22.01	21.30	21.43	NAN	20.46
C7orf50	Q9BRJ6	4	NAN	20.08	21.03	21.21	21.41	21.77	21.28	20.78	NAN	20.77
C9orf78	Q9NZ63	7	NAN	NAN	21.03	21.73	20.91	21.11	21.55	21.60	20.75	20.90
CACYBP	Q9HB71	4	NAN	NAN	NAN	NAN	20.49	20.45	NAN	NAN	19.72	NAN
CALD1	Q05682	6	NAN	NAN	NAN	20.65	19.54	19.87	20.69	20.43	21.35	21.38
CALM1	P0DP23	10	NAN	NAN	22.82	NAN	21.31	NAN	21.91	24.53	21.98	21.98
CALR	P27797	5	NAN	NAN	NAN	NAN	NAN	NAN	19.98	21.91	20.29	20.69
CALU	O43852	6	NAN	NAN	NAN	NAN	19.00	NAN	19.12	21.53	NAN	NAN
CAMK2D	Q13557	4	NAN	NAN	NAN	NAN	NAN	NAN	19.70	19.50	NAN	NAN
CAND1	Q86VP6	6	NAN	NAN	19.96	NAN	19.22	19.62	19.58	20.11	NAN	19.56
CANX	P27824	12	NAN	NAN	NAN	NAN	NAN	NAN	21.19	22.02	21.99	21.60
CAPG	Q9BPX3	7	NAN	NAN	NAN	NAN	20.24	20.05	20.08	22.84	NAN	19.76
CAPN1	P07384	15	21.24	19.26	21.45	NAN	20.02	20.81	21.26	23.01	21.28	21.11
CAPZA1	P52907	10	NAN	NAN	NAN	NAN	20.27	20.12	NAN	22.16	NAN	20.59
CAPZB	P47756	7	NAN	NAN	NAN	20.68	19.69	20.38	20.45	23.00	20.46	20.55
CARM1	Q86X55	11	NAN	NAN	NAN	22.72	23.62	23.78	23.27	23.07	22.55	22.55
CBFA2T2	O43439	9	20.36	NAN	NAN	NAN	21.83	22.14	21.02	21.15	NAN	NAN
CBFB	Q13951	5	NAN	NAN	NAN	22.29	22.56	22.65	21.92	21.52	20.65	20.90
CBR1	P16152	11	NAN	NAN	21.78	NAN	21.26	21.72	21.56	22.83	NAN	21.88
CBX1	P83916	8	22.49	22.65	22.18	22.78	23.78	23.80	23.63	23.09	23.18	23.11
CBX3	Q13185	9	26.00	24.80	24.92	25.80	25.10	25.58	25.49	25.10	25.18	25.39
CBX4	O00257	7	NAN	NAN	NAN	21.53	21.19	20.73	21.36	20.76	NAN	19.87
CBX5	P45973	9	25.43	24.23	22.41	23.68	23.38	23.51	23.77	23.08	23.23	23.67
CBX8	Q9HC52	2	NAN	NAN	NAN	NAN	19.22	NAN	NAN	NAN	19.36	19.26
CCAR2	Q8N163	13	21.95	21.53	20.29	NAN	20.37	19.97	21.33	20.14	21.06	21.15

CCDC137	Q6PK04	4	NAN	NAN	NAN	NAN	23.45	23.86	NAN	NAN	NAN	NAN
CCDC82	Q8N4S0	8	NAN	NAN	NAN	NAN	20.79	20.98	18.90	18.85	NAN	NAN
CCDC86	Q9H6F5	7	NAN	NAN	NAN	NAN	21.51	21.12	21.44	20.71	21.20	NAN
CCND1	P24385	7	NAN	NAN	NAN	NAN	19.76	19.98	20.05	20.25	19.74	19.99
CCNH	P51946	9	NAN	NAN	NAN	NAN	21.54	21.54	21.18	20.92	NAN	20.98
CCNT1	O60563	6	NAN	NAN	NAN	NAN	19.71	19.58	19.48	19.74	NAN	NAN
CCT3	P49368	16	NAN	NAN	NAN	NAN	23.16	22.86	22.11	23.00	21.85	21.98
CCT5	P48643	6	NAN	NAN	NAN	NAN	19.00	NAN	19.12	21.53	NAN	NAN
CCT6A	P40227	2	NAN	NAN	NAN	NAN	NAN	NAN	18.56	20.51	NAN	NAN
CCT8	P50990	9	NAN	NAN	NAN	NAN	20.74	20.29	20.84	22.02	NAN	20.95
CCZ1	P86791	9	NAN	NAN	NAN	NAN	20.42	20.16	19.59	19.80	19.61	NAN
CD2BP2	O95400	7	NAN	NAN	NAN	NAN	21.95	22.21	21.04	21.32	NAN	NAN
CDC16	Q13042	3	NAN	NAN	NAN	NAN	19.27	18.79	19.32	NAN	NAN	NAN
CDC20	Q12834	6	NAN	NAN	NAN	NAN	21.17	21.36	21.28	20.79	NAN	NAN
CDC23	Q9UJX2	18	NAN	NAN	NAN	NAN	23.61	23.85	21.74	21.72	NAN	19.37
CDC37	Q16543	8	NAN	NAN	21.64	22.70	22.08	22.33	21.74	21.39	21.93	22.22
CDC40	O60508	12	NAN	NAN	NAN	21.13	22.14	22.14	21.37	20.86	20.21	20.40
CDC5L	Q99459	13	NAN	NAN	NAN	NAN	20.36	NAN	21.07	20.69	20.88	20.86
CDC73	Q6P1J9	5	NAN	NAN	NAN	NAN	19.30	NAN	19.33	18.94	NAN	19.15
CDCA8	Q53HL2	8	21.86	21.15	NAN	NAN	19.21	19.50	21.07	21.24	NAN	20.32
CDK1	P06493	11	NAN	21.43	21.71	22.91	22.39	22.62	22.77	21.86	21.45	NAN
CDK11A	Q9UQ88	9	NAN	NAN	NAN	21.10	21.47	20.74	21.37	20.42	20.74	20.40
CDK2AP1	O14519	4	20.99	NAN	20.74	20.30	21.32	21.26	21.69	21.02	20.08	20.36
CDK4	P11802	7	NAN	NAN	NAN	NAN	20.79	21.02	20.22	NAN	NAN	20.11
CDK7	P50613	12	NAN	NAN	NAN	21.56	21.98	22.14	21.62	21.33	NAN	20.85
CDK8	P49336	3	NAN	NAN	NAN	NAN	19.76	19.23	18.67	NAN	NAN	NAN
CDKN1A	P38936	4	NAN	NAN	NAN	20.74	22.06	21.80	21.27	20.92	19.92	NAN
CDKN2AIP	Q9NXV6	13	NAN	NAN	NAN	NAN	21.44	21.11	20.79	20.63	NAN	NAN
CDYL	Q9Y232	8	NAN	NAN	NAN	NAN	20.17	19.90	20.77	19.89	NAN	NAN
CEBPB	P17676	9	NAN	NAN	NAN	23.61	23.87	24.23	22.58	22.60	NAN	21.25
CECR2	Q9BXF3	7	22.13	22.16	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
CENPB	P07199	3	NAN	NAN	NAN	21.05	19.83	NAN	21.39	NAN	21.13	21.08
CENPC	Q03188	8	NAN	NAN	NAN	19.34	NAN	18.12	NAN	NAN	19.39	20.37
CENPV	Q7Z7K6	6	NAN	22.65	19.34	21.40	19.38	19.90	20.99	20.05	19.37	21.19
CETN2	P41208	4	NAN	NAN	NAN	NAN	19.89	20.07	19.34	NAN	NAN	19.92
CFAP20	Q9Y6A4	5	NAN	NAN	NAN	NAN	20.45	20.02	NAN	20.48	20.05	20.34
CFDP1	Q9UEE9	3	NAN	NAN	NAN	NAN	18.52	19.51	NAN	NAN	NAN	NAN
CFL1	P23528	12	23.74	23.78	23.97	24.18	24.49	24.22	24.54	24.86	24.20	24.46
CGGBP1	Q9UFW8	4	NAN	NAN	NAN	NAN	20.10	19.69	20.38	20.07	NAN	NAN
CHAMP1	Q96JM3	11	NAN	NAN	NAN	21.24	21.64	21.76	21.59	21.01	NAN	20.77
CHD1	O14646	20	NAN	NAN	NAN	20.32	22.04	22.24	21.94	21.03	20.84	20.67
CHD3	Q12873	24	NAN	NAN	NAN	21.33	21.32	20.57	21.70	20.70	NAN	20.49
CHD4	Q14839	70	26.02	25.15	24.59	25.53	25.53	25.74	25.72	25.18	24.59	24.74
CHD7	Q9P2D1	22	20.32	NAN	NAN	NAN	21.71	20.69	19.68	18.64	NAN	NAN
CHD8	Q9HCK8	16	NAN	NAN	NAN	NAN	20.30	20.37	19.90	20.53	NAN	NAN
CHD9	Q3L8U1	28	NAN	NAN	NAN	NAN	23.30	22.48	21.52	20.59	NAN	20.15
CHERP	Q8IWX8	9	NAN	NAN	NAN	21.42	21.84	22.35	21.96	21.75	21.53	21.60
CHTF8	P0CG13	8	NAN	NAN	NAN	21.66	23.27	23.93	22.13	22.53	NAN	NAN
CIAO1	O76071	10	NAN	NAN	20.37	21.63	22.69	23.22	22.17	22.36	NAN	21.26
CIRBP	Q14011	2	NAN	NAN	NAN	NAN	NAN	19.99	20.06	19.63	NAN	NAN
CIZ1	Q9ULV3	6	NAN	NAN	NAN	NAN	NAN	NAN	20.18	19.93	NAN	NAN
CKAP4	Q07065	21	NAN	NAN	19.61	NAN	NAN	20.25	20.66	23.19	20.53	22.50
CKB	P12277	7	NAN	NAN	NAN	NAN	19.33	19.30	20.40	20.23	NAN	20.08
CLIC1	O00299	10	NAN	NAN	22.99	22.46	22.53	22.73	22.48	23.43	22.55	22.90
CLIC3	O95833	11	NAN	NAN	20.65	NAN	24.23	24.15	21.99	23.54	20.96	21.13
CLIC4	Q9Y696	7	NAN	NAN	NAN	NAN	NAN	20.25	19.99	20.28	20.16	20.03
CLOCK	O15516	3	NAN	NAN	NAN	NAN	19.37	19.44	NAN	NAN	NAN	NAN
CLP1	Q92989	3	NAN	NAN	NAN	NAN	20.09	19.90	NAN	NAN	NAN	NAN
CLTC	Q00610	33	NAN	NAN	23.80	23.82	22.60	22.53	23.03	24.01	23.71	23.80
CMAS	Q8NFW8	12	NAN	NAN	NAN	21.79	22.74	22.60	22.59	22.41	23.00	23.12
CMBL	Q96DG6	15	NAN	NAN	19.94	22.77	23.26	23.13	23.24	23.31	22.31	22.53
CMPK1	P30085	3	NAN	NAN	NAN	19.66	NAN	19.11	NAN	21.15	19.78	19.64
CMTR1	Q8N1G2	6	NAN	NAN	20.53	20.86	20.13	20.68	20.21	20.06	21.10	20.86
CNBP	P62633	9	22.59	22.08	21.60	22.59	22.50	22.46	21.94	21.81	21.43	21.79
CNN1	P51911	9	NAN	NAN	22.30	22.78	22.05	22.50	22.85	22.77	22.90	23.08
CNN2	Q99439	12	NAN	NAN	23.55	23.03	23.59	23.65	23.59	23.46	23.35	23.50
CNN3	Q15417	10	NAN	NAN	NAN	21.33	21.15	21.50	22.02	21.32	21.87	21.96
CNOT1	A5YKK6	14	NAN	NAN	22.21	21.81	20.29	20.85	20.98	20.84	20.72	20.47
COL1A1	P02452	8	23.40	NAN	NAN	NAN	21.84	21.63	21.23	NAN	22.07	21.83
COMMD9	Q9P000	2	NAN	NAN	NAN	NAN	19.16	19.35	18.68	NAN	NAN	NAN

COMT	P21964	5	NAN	NAN	NAN	NAN	NAN	NAN	22.06	21.93	22.08	21.03
COPA	P53621	11	NAN	NAN	NAN	NAN	NAN	NAN	22.73	21.38	NAN	21.37
CPNE2	Q96FN4	4	NAN	NAN	NAN	NAN	18.67	18.59	NAN	18.49	NAN	NAN
CPNE3	O75131	10	NAN	20.21	21.46	21.71	22.02	22.42	22.11	22.96	22.02	22.02
CPNE7	Q9UBL6	5	NAN	NAN	NAN	NAN	18.80	19.56	NAN	NAN	NAN	NAN
CPNE8	Q86YQ8	5	NAN	NAN	NAN	NAN	19.22	19.49	NAN	NAN	NAN	NAN
CPSF1	Q10570	8	NAN	NAN	NAN	NAN	20.26	20.02	20.74	NAN	NAN	20.45
CPSF3L	Q5TA45	4	NAN	NAN	NAN	NAN	19.34	19.80	19.56	19.33	NAN	NAN
CPSF6	Q16630	6	NAN	NAN	NAN	NAN	20.36	20.71	22.24	20.92	NAN	20.70
CPSF7	Q8N684	13	NAN	22.20	21.59	22.43	22.87	23.46	22.94	23.01	20.86	21.77
CRABP2	P29373	5	NAN	NAN	NAN	NAN	20.25	20.07	20.40	23.06	NAN	NAN
CREB1	P16220	4	NAN	NAN	NAN	NAN	21.31	20.93	20.53	NAN	NAN	NAN
CREB5	Q02930	3	NAN	NAN	NAN	NAN	19.52	20.69	NAN	NAN	NAN	NAN
CREBBP	Q92793	38	NAN	NAN	NAN	22.03	23.57	23.56	22.37	22.23	NAN	20.24
CRIP1	P50238	4	NAN	NAN	NAN	20.93	21.62	22.38	20.89	21.14	21.13	21.16
CRIP2	P52943	7	NAN	NAN	21.87	22.86	23.55	23.37	22.92	23.37	22.50	22.77
CRK	P46108	4	NAN	NAN	NAN	NAN	20.22	20.01	19.91	19.75	NAN	20.00
CRKL	P46109	5	NAN	NAN	NAN	21.53	22.19	21.55	21.36	20.97	20.93	NAN
CROP	O95232	6	20.62	21.26	NAN	NAN	19.59	19.12	21.43	20.24	21.18	20.58
CRTC2	Q53ET0	13	NAN	NAN	NAN	NAN	23.58	23.35	22.20	21.75	NAN	20.13
CRTC3	Q6UUV7	7	NAN	NAN	NAN	NAN	21.59	21.53	21.26	20.70	NAN	NAN
CRYAB	P02511	9	NAN	NAN	24.41	24.24	23.41	23.61	24.15	24.00	25.97	25.77
CSE1L	P55060	26	22.91	22.47	21.36	23.02	23.25	23.14	23.98	23.44	23.37	23.20
CSNK1A1	P48729	6	NAN	NAN	NAN	NAN	21.67	21.37	20.86	21.22	20.42	20.65
CSNK1D	P48730	9	NAN	NAN	NAN	NAN	19.29	20.28	NAN	NAN	NAN	NAN
CSNK1E	P49674	9	NAN	NAN	20.36	20.80	22.66	23.22	21.60	22.06	NAN	20.27
CSNK2A1	P68400	12	NAN	21.14	21.27	21.98	22.67	22.99	21.94	21.93	21.20	NAN
CSNK2A2	P19784	11	NAN	NAN	NAN	NAN	21.64	21.81	21.77	21.86	20.90	20.25
CSNK2B	P67870	6	21.54	21.19	21.38	22.17	22.61	22.68	22.03	22.26	21.55	22.13
CSTA	P01040	4	22.77	21.27	21.91	22.21	20.20	19.99	20.69	24.74	22.54	22.13
CSTF1	Q05048	10	20.72	NAN	21.44	21.66	23.37	23.22	23.52	22.52	NAN	22.52
CSTF2	P33240	6	NAN	NAN	NAN	NAN	19.29	NAN	19.60	19.92	19.47	NAN
CSTF2T	Q9H0L4	8	NAN	NAN	NAN	21.19	20.78	20.32	21.44	21.27	20.93	NAN
CSTF3	Q12996	12	NAN	20.81	21.70	22.08	20.96	21.01	22.16	21.21	NAN	21.32
CTBP1	Q13363	15	23.16	22.99	23.17	24.26	25.13	25.50	24.64	24.60	23.80	24.25
CTBP2	P56545	14	24.23	24.20	22.70	24.12	24.92	25.01	24.79	24.13	23.69	23.83
CTNNA1	P35221	5	NAN	NAN	NAN	NAN	NAN	NAN	19.90	20.15	NAN	NAN
CTNNBL1	Q8WYA6	9	NAN	NAN	NAN	21.49	20.42	20.81	20.75	20.30	20.60	21.05
CTNND1	O60716	11	NAN	NAN	NAN	NAN	21.03	21.32	20.78	NAN	NAN	NAN
CTR9	Q6PD62	3	NAN	NAN	NAN	NAN	18.84	19.21	NAN	NAN	NAN	NAN
CTSB	P07858	5	NAN	NAN	NAN	19.94	NAN	NAN	19.34	23.10	19.42	19.68
CTTN	Q14247	7	NAN	NAN	NAN	NAN	NAN	NAN	18.63	18.32	18.30	NAN
CTU1	Q7Z7A3	4	NAN	NAN	NAN	NAN	20.43	20.88	NAN	19.81	NAN	NAN
CUX1	Q13948	26	NAN	NAN	20.36	NAN	23.17	22.30	22.27	21.16	20.62	NAN
CWF19L1	Q69YN2	4	NAN	NAN	NAN	NAN	19.60	19.30	19.70	19.65	NAN	NAN
CXXC5	Q7LFL8	4	NAN	NAN	NAN	NAN	20.65	19.53	18.89	18.84	NAN	NAN
CYB5R3	P00387	10	NAN	NAN	NAN	22.60	20.72	20.30	22.06	21.47	23.38	22.96
CYFIP1	Q7L576	15	NAN	NAN	NAN	20.24	20.45	20.83	20.41	21.13	20.13	20.25
DAXX	Q9UER7	7	NAN	NAN	NAN	NAN	21.61	21.73	22.12	NAN	NAN	NAN
DAZAP1	Q96EP5	16	22.26	NAN	22.19	21.69	23.04	22.97	23.21	22.71	22.32	21.40
DBI	P07108	3	NAN	NAN	NAN	NAN	NAN	NAN	19.43	22.20	NAN	NAN
DBR1	Q9UK59	4	NAN	NAN	NAN	20.18	20.91	21.22	20.37	20.06	20.13	NAN
DCAF13	Q9NV06	4	NAN	NAN	NAN	NAN	19.27	19.71	19.12	NAN	19.08	NAN
DCAF4	Q8WV16	4	NAN	NAN	NAN	NAN	20.43	19.72	NAN	NAN	NAN	NAN
DCAF7	P61962	16	22.05	NAN	23.30	23.57	26.22	26.11	25.41	25.13	23.22	23.46
DCUN1D5	Q9BTE7	3	NAN	NAN	NAN	NAN	NAN	19.71	19.39	19.50	NAN	NAN
DDB1	Q16531	40	22.15	22.23	NAN	24.18	25.11	25.33	24.22	23.57	23.47	23.94
DDB2	Q92466	13	NAN	NAN	NAN	21.29	23.75	23.78	21.09	19.06	NAN	21.15
DDOST	P39656	5	NAN	NAN	NAN	NAN	NAN	NAN	19.90	21.49	NAN	NAN
DDX1	Q92499	22	20.93	23.31	24.15	24.29	23.77	23.62	23.41	23.64	23.60	23.45
DDX17	Q92841	26	25.70	26.87	23.90	24.92	25.15	25.12	25.00	24.72	24.65	24.67
DDX21	Q9NR30	16	22.00	22.53	NAN	21.51	21.07	20.88	22.45	21.35	22.22	22.36
DDX39A	O00148	15	NAN	NAN	NAN	21.05	20.61	20.15	21.14	20.87	21.26	21.34
DDX39B	Q13838	15	24.72	25.28	23.17	24.22	23.47	23.27	24.25	23.90	23.97	24.18
DDX3X	O00571	17	22.44	22.22	21.87	20.69	21.34	21.78	22.61	23.51	22.44	22.50
DDX42	Q86XP3	15	NAN	NAN	NAN	21.56	21.59	21.39	21.81	21.30	21.73	21.52
DDX47	Q9H0S4	9	NAN	21.29	NAN	20.18	20.98	20.90	20.65	20.32	NAN	20.31
DDX48	P38919	22	22.20	24.43	24.90	25.67	24.85	24.92	25.84	25.53	24.48	25.54
DDX49	Q9Y6V7	7	NAN	NAN	21.33	21.61	21.45	22.05	21.08	20.98	20.86	20.93
DDX5	P17844	28	26.57	27.16	25.94	26.60	27.69	27.69	27.23	26.81	26.57	26.60

DEK	P35659	10	23.87	23.38	22.07	23.69	22.39	22.71	23.61	23.00	23.39	23.66
DHX15	O43143	28	24.27	24.09	23.82	25.19	24.86	25.09	25.28	24.68	25.22	25.50
DHX16	O60231	17	NAN	NAN	NAN	NAN	21.87	21.98	21.65	21.43	21.18	21.13
DHX34	Q14147	9	NAN	NAN	NAN	NAN	21.07	21.25	NAN	NAN	NAN	NAN
DHX36	Q9H2U1	20	NAN	NAN	NAN	21.04	23.61	23.80	22.15	22.31	21.20	21.87
DHX37	Q8IY37	11	NAN	NAN	20.73	NAN	19.99	19.29	19.63	NAN	NAN	20.09
DHX38	Q92620	13	NAN	NAN	NAN	NAN	21.56	21.07	21.19	20.67	21.13	NAN
DHX9	Q08211	42	25.95	27.14	25.50	26.60	26.95	26.91	27.01	26.53	26.77	26.71
DIMT1	Q9UNQ2	7	NAN	NAN	NAN	NAN	20.85	20.83	21.28	20.34	NAN	20.80
DIS3	Q9Y2L1	31	NAN	20.60	21.32	23.77	23.48	23.74	23.70	23.70	22.40	23.35
DLX1	P56177	4	NAN	NAN	NAN	NAN	NAN	20.18	20.23	20.57	NAN	NAN
DLX3	O60479	4	NAN	NAN	NAN	NAN	NAN	19.17	20.00	19.93	NAN	NAN
DMAP1	Q9NPF5	7	NAN	NAN	NAN	NAN	19.53	19.98	NAN	19.43	NAN	NAN
DNAAF5	Q86Y56	8	NAN	NAN	NAN	NAN	20.50	20.78	20.49	20.23	NAN	19.70
DNAJA1	P31689	17	20.63	21.68	23.98	25.67	25.90	25.94	25.55	25.42	24.75	25.69
DNAJA2	O60884	15	21.01	21.38	24.15	24.44	24.38	24.58	24.32	24.01	23.87	23.90
DNAJB1	P25685	14	NAN	NAN	23.55	23.56	25.89	25.91	23.92	24.20	23.82	23.66
DNAJB2	P25686	7	NAN	NAN	NAN	NAN	20.52	21.50	19.96	20.57	NAN	19.88
DNAJB4	Q9UDY4	9	NAN	NAN	NAN	NAN	22.31	22.47	19.63	19.64	19.89	19.33
DNAJB6	O75190	16	22.57	21.71	23.60	24.11	27.01	27.15	24.62	25.07	23.77	23.67
DNAJC7	Q99615	23	NAN	NAN	NAN	21.68	24.99	24.77	22.49	22.49	NAN	21.33
DNAJC8	O75937	10	21.72	21.69	22.30	22.77	22.79	22.93	22.67	22.44	22.12	22.32
DNAJC9	Q8WXX5	4	NAN	NAN	NAN	NAN	NAN	19.63	20.50	19.97	19.76	NAN
DNCL1	P63167	3	23.47	NAN	22.20	22.81	21.83	22.82	22.79	23.28	22.18	22.86
DNMT1	P26358	10	NAN	NAN	NAN	NAN	NAN	NAN	20.13	20.09	NAN	20.42
DNMT3A	Q9Y6K1	4	22.37	22.23	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
DNMT3B	Q9UBC3	23	26.39	25.36	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
DNTTIP1	Q9H147	15	NAN	NAN	NAN	21.79	24.69	24.75	23.46	23.19	NAN	NAN
DNTTIP2	Q5QJE6	21	19.67	19.53	20.17	21.30	23.78	23.05	21.56	21.12	21.48	19.95
DPF2	Q92785	17	22.67	22.83	22.92	23.01	23.95	24.27	23.45	22.50	21.30	21.95
DPH2	Q9BQC3	6	NAN	NAN	20.70	NAN	20.37	20.13	NAN	NAN	NAN	NAN
DR1	Q01658	4	NAN	NAN	NAN	NAN	21.62	21.72	21.22	20.53	NAN	NAN
DRAP1	Q14919	6	NAN	NAN	21.21	NAN	22.27	21.47	21.99	20.83	20.89	NAN
DROSHA	Q9NRR4	6	NAN	NAN	NAN	NAN	19.40	19.43	NAN	NAN	NAN	NAN
DSC3	Q02487	12	19.89	NAN	24.39	NAN	20.86	NAN	19.70	21.05	21.27	NAN
DSTN	P60981	7	NAN	NAN	21.69	21.80	21.27	21.74	21.77	22.27	21.95	22.29
DTX2	Q86UW9	11	NAN	NAN	NAN	NAN	22.81	23.11	21.14	21.43	NAN	NAN
DUSP11	O75319	9	NAN	NAN	NAN	NAN	21.68	22.42	18.94	18.86	NAN	18.34
DUSP14	O95147	5	NAN	NAN	20.91	NAN	22.10	21.94	NAN	21.28	NAN	NAN
DUSP23	Q9BVJ7	8	NAN	NAN	21.06	21.01	22.29	22.39	21.14	21.65	20.77	21.11
EBF1	Q9UH73	14	NAN	NAN	22.70	22.09	23.54	23.74	22.87	22.64	21.17	22.55
EBF3	Q9H4W6	13	NAN	NAN	NAN	NAN	20.03	20.28	20.20	20.22	NAN	NAN
EED	O75530	3	NAN	NAN	NAN	NAN	19.47	20.11	NAN	19.98	NAN	20.45
EEF1G	P26641	10	NAN	NAN	22.61	20.69	20.89	20.20	19.80	23.38	20.81	21.57
EEF2	P13639	38	24.25	24.35	25.16	24.35	23.34	23.32	24.56	26.68	24.49	24.48
EFTUD2	Q15029	16	21.15	21.15	20.64	20.79	20.48	20.68	21.64	20.64	21.59	21.31
EGR1	P18146	10	NAN	NAN	21.40	21.67	24.13	24.02	21.27	NAN	NAN	NAN
EHD1	Q9NZN3	10	NAN	NAN	NAN	NAN	NAN	NAN	19.61	21.87	NAN	NAN
EHMT1	Q9H9B1	9	21.34	NAN	NAN	NAN	20.66	20.09	20.59	NAN	NAN	NAN
EHMT2	Q96KQ7	8	NAN	21.01	NAN	NAN	20.97	20.26	20.38	NAN	NAN	NAN
EIF2S1	P05198	10	NAN	NAN	NAN	NAN	20.13	20.05	20.67	21.56	NAN	20.25
EIF3D	O15371	15	NAN	NAN	21.26	21.60	23.98	24.52	22.58	23.49	21.03	21.49
EIF3E	P60228	6	NAN	NAN	NAN	NAN	21.41	21.29	20.61	21.22	NAN	NAN
EIF3H	O15372	2	NAN	NAN	NAN	NAN	19.18	19.59	NAN	NAN	NAN	NAN
EIF3K	Q9UBQ5	3	NAN	NAN	NAN	NAN	NAN	18.86	18.96	19.22	NAN	19.07
EIF3L	Q9Y262	8	NAN	NAN	NAN	NAN	20.94	20.94	20.27	20.76	NAN	20.38
EIF3M	Q7L2H7	2	NAN	NAN	NAN	NAN	NAN	17.89	18.02	18.40	NAN	NAN
EIF3S2	Q13347	10	NAN	NAN	NAN	NAN	22.27	22.76	22.32	21.85	21.42	21.67
EIF3S8	Q99613	3	NAN	NAN	NAN	NAN	NAN	NAN	18.88	18.58	18.90	18.41
EIF4A1	P60842	21	23.75	24.40	23.66	23.79	24.68	24.77	24.69	25.17	24.78	24.62
EIF4E2	O60573	2	NAN	NAN	NAN	NAN	17.53	18.83	NAN	NAN	NAN	NAN
EIF4H	Q15056	7	20.72	NAN	21.53	22.17	22.52	23.06	22.41	22.82	22.20	22.79
EIF5A	P63241	10	22.75	25.54	24.78	24.67	24.12	24.67	24.42	24.42	24.18	24.29
EIF6	P56537	8	NAN	NAN	23.95	NAN	20.64	21.31	20.80	23.01	NAN	NAN
ELAC2	Q9BQ52	15	NAN	NAN	20.30	21.23	21.94	22.33	21.25	21.51	20.77	21.63
ELAVL1	Q15717	9	23.14	23.84	23.04	23.73	24.16	23.91	23.52	23.45	23.27	23.29
ELF4	Q99607	2	NAN	NAN	NAN	NAN	18.82	18.83	NAN	NAN	NAN	NAN
ELMSAN1	Q6PJG2	42	NAN	NAN	21.70	23.74	26.08	27.05	24.72	25.06	20.06	21.64
ELOA	Q14241	4	NAN	NAN	NAN	NAN	19.22	19.40	19.32	NAN	NAN	NAN
ELOC	Q15369	4	NAN	NAN	NAN	21.94	20.50	20.00	NAN	20.36	NAN	20.17

EMX2	Q04743	7	NAN	NAN	22.13	22.40	22.11	21.76	21.77	21.89	21.24	NAN
ENGASE	Q8NFI3	19	NAN	NAN	NAN	NAN	22.41	23.17	21.62	21.89	20.56	21.15
EP300	Q09472	40	20.61	19.71	22.70	22.68	25.46	25.67	23.80	23.33	21.28	21.95
EPM2AIP1	Q7L775	9	NAN	NAN	NAN	NAN	21.09	21.24	20.82	NAN	NAN	20.78
ERCC2	P18074	6	NAN	NAN	NAN	21.06	21.48	21.14	21.28	20.29	NAN	20.46
ERCC3	P19447	14	NAN	NAN	NAN	NAN	20.75	20.49	20.55	19.75	NAN	20.17
ERCC4	Q92889	5	NAN	NAN	NAN	NAN	18.82	NAN	19.05	18.74	NAN	NAN
ERH	P84090	3	22.96	23.15	21.46	22.83	22.18	22.04	22.49	22.32	22.14	22.52
ESD	P10768	7	NAN	NAN	NAN	NAN	22.09	21.90	21.75	21.70	NAN	21.30
ESRRA	P11474	11	NAN	NAN	22.98	22.35	23.25	22.48	21.91	22.32	21.30	20.95
ESS2	Q96DF8	20	NAN	NAN	NAN	22.23	24.06	24.28	23.57	22.95	20.65	21.10
ETF1	P62495	7	NAN	NAN	NAN	NAN	20.47	21.11	21.13	21.50	20.56	20.67
ETS1	P14921	6	NAN	NAN	NAN	NAN	19.93	20.81	NAN	NAN	NAN	NAN
ETV4	P43268	14	NAN	NAN	21.65	21.71	22.83	23.10	22.00	21.59	NAN	NAN
ETV5	P41161	7	NAN	NAN	NAN	NAN	22.07	22.31	21.41	21.47	NAN	NAN
ETV6	P41212	11	NAN	21.67	NAN	22.02	21.40	22.35	21.48	21.28	NAN	20.75
EWSR1	Q01844	8	24.22	23.98	25.16	25.78	26.63	27.09	26.20	26.60	24.60	24.90
EXOSC5	Q9NQT4	2	NAN	NAN	NAN	NAN	19.88	20.19	19.54	19.37	NAN	19.36
EYA3	Q99504	9	NAN	NAN	NAN	NAN	21.29	21.40	21.06	20.86	NAN	NAN
FAM168A	Q92567	6	NAN	NAN	NAN	NAN	23.52	23.44	NAN	NAN	NAN	NAN
FAM207A	Q9NSI2	6	NAN	NAN	NAN	NAN	22.43	22.57	20.74	21.35	20.64	20.53
FAM216A	Q8WUB2	3	NAN	NAN	NAN	NAN	19.04	19.50	NAN	NAN	NAN	NAN
FAM222B	Q8WU58	4	NAN	NAN	NAN	NAN	21.75	21.69	20.35	19.97	NAN	NAN
FAM64A	Q9BSJ6	5	NAN	NAN	NAN	NAN	19.49	19.69	19.54	19.25	NAN	NAN
FAM83H	Q6ZRV2	14	NAN	NAN	NAN	NAN	20.46	21.16	20.56	21.73	NAN	19.70
FAM98A	Q8NCA5	10	NAN	NAN	NAN	22.21	22.15	22.39	21.66	21.63	NAN	21.52
FAM98B	Q52LJ0	9	NAN	NAN	NAN	21.02	21.34	20.78	21.23	20.53	20.88	21.24
FARSLA	Q9Y285	11	NAN	NAN	NAN	NAN	22.04	21.95	20.65	20.39	20.04	19.55
FASN	P49327	20	19.60	20.56	20.53	NAN	NAN	NAN	18.62	23.39	NAN	NAN
FBL	P22087	14	23.55	23.52	24.43	25.26	25.59	25.89	25.17	25.01	23.94	24.45
FBRS	Q9HAH7	13	NAN	NAN	22.04	23.03	24.92	25.08	23.63	23.67	NAN	21.98
FBRSL1	Q9HCM7	21	NAN	NAN	21.57	21.58	24.59	24.71	23.61	23.02	NAN	NAN
FBXO7	Q9Y3I1	4	NAN	NAN	NAN	NAN	19.54	NAN	NAN	19.42	19.56	19.41
FCGRT	P55899	3	22.42	NAN	21.84	22.21	NAN	NAN	NAN	NAN	NAN	NAN
FEN1	P39748	8	NAN	NAN	NAN	21.87	21.58	22.07	22.39	21.51	21.61	21.68
FGF2	P09038	5	NAN	NAN	NAN	22.78	22.57	22.80	22.73	22.96	23.07	23.52
FHL3	Q13643	12	NAN	NAN	22.81	23.73	24.51	24.53	23.71	23.71	22.72	23.21
FIP1L1	Q6UN15	5	NAN	NAN	NAN	NAN	19.32	NAN	19.79	19.17	20.24	NAN
FKBP1A	P62942	5	NAN	21.04	22.42	23.19	23.20	22.95	22.57	22.49	22.80	22.68
FLI1	Q01543	10	NAN	NAN	NAN	21.18	22.56	23.17	21.31	21.43	19.76	NAN
FLNB	O75369	17	NAN	NAN	NAN	NAN	NAN	NAN	18.78	22.23	NAN	NAN
FLNC	Q14315	58	NAN	NAN	23.41	23.99	21.87	22.33	23.55	22.87	24.66	24.71
FOS	P01100	6	NAN	NAN	22.06	NAN	20.70	20.93	20.62	20.17	NAN	NAN
FOSB	P53539	5	NAN	NAN	22.23	22.03	22.32	21.87	21.86	22.01	NAN	20.58
FOSL1	P15407	11	NAN	NAN	22.31	23.33	25.94	25.88	24.16	23.93	22.66	23.11
FOSL2	P15408	8	NAN	NAN	NAN	21.75	23.47	23.67	22.50	22.62	21.18	21.89
FOXC2	Q99958	6	NAN	NAN	NAN	NAN	19.31	NAN	18.81	19.01	NAN	NAN
FOXF2	Q12947	3	NAN	NAN	NAN	NAN	19.18	19.48	NAN	18.56	NAN	NAN
FOXJ2	Q9P0K8	8	NAN	NAN	22.07	22.91	23.42	23.32	22.94	22.80	NAN	22.11
FOXJ3	Q9UPW0	8	NAN	NAN	NAN	21.93	22.96	23.37	22.22	22.32	NAN	NAN
FOXL2	P58012	5	NAN	NAN	NAN	NAN	21.10	22.03	NAN	20.38	NAN	20.46
FOXO3	O43524	2	NAN	NAN	NAN	NAN	18.84	18.51	NAN	NAN	NAN	NAN
FOXP1	Q9H334	16	NAN	NAN	NAN	22.09	23.44	23.45	22.54	22.18	NAN	NAN
FOXP4	Q8IVH2	9	NAN	NAN	20.73	21.63	22.56	22.30	21.95	21.37	NAN	20.64
FPGS	Q05932	5	NAN	NAN	NAN	NAN	20.87	21.13	NAN	NAN	NAN	NAN
FRG1	Q14331	8	NAN	NAN	20.88	21.64	21.52	21.55	22.03	21.34	21.14	21.22
FSCN1	Q16658	9	21.39	21.38	22.20	21.80	21.58	21.12	21.86	22.19	21.99	22.18
FTO	Q9C0B1	13	NAN	NAN	20.95	20.20	20.52	20.37	20.72	20.32	NAN	20.68
FUBP1	Q96AE4	28	25.20	26.28	25.20	25.43	25.61	25.72	25.64	25.56	24.67	24.72
FUBP3	Q96I24	24	NAN	23.13	23.03	24.05	24.22	24.04	24.72	24.52	23.32	22.87
FUS	P35637	12	24.56	25.22	25.19	25.48	26.04	26.08	26.09	25.95	24.52	24.49
FXR1	P51114	4	NAN	21.33	NAN	NAN	NAN	19.70	20.68	19.53	20.54	20.83
G3BP	Q13283	4	20.28	21.09	NAN	NAN	18.53	NAN	19.72	19.87	NAN	NAN
GALK1	P51570	7	NAN	NAN	NAN	NAN	21.77	21.30	21.10	20.66	NAN	NAN
GAR1	Q9NY12	3	NAN	NAN	NAN	NAN	22.07	22.07	20.88	21.05	20.02	20.21
GATA2	P23769	11	NAN	NAN	22.33	22.29	22.90	23.00	23.00	23.19	21.00	21.63
GATA6	Q92908	7	NAN	NAN	NAN	21.78	22.26	22.48	21.77	21.69	NAN	NAN
GATAD2A	Q86YP4	23	24.26	23.35	22.85	23.82	23.64	23.75	23.63	23.36	22.73	23.09
GATAD2B	Q8WXI9	16	22.06	21.89	21.91	23.27	24.02	23.83	23.48	22.95	22.09	22.47
GBE1	P32455	27	NAN	NAN	24.21	25.62	25.78	25.96	25.53	25.60	24.84	25.16

GDI2	P50395	12	NAN	19.01	20.82	NAN	20.06	20.33	21.03	23.57	19.12	20.25
GFPT1	Q06210	4	NAN	NAN	NAN	NAN	NAN	NAN	NAN	19.75	20.49	20.07
GGCT	O75223	10	22.16	22.39	24.31	21.76	NAN	19.73	21.52	25.18	21.52	21.52
GGH	Q92820	4	NAN	NAN	NAN	NAN	NAN	NAN	20.13	20.88	NAN	NAN
GIPC1	O14908	12	NAN	NAN	21.03	22.05	22.57	22.25	21.87	22.15	NAN	20.53
GIT2	Q14161	3	NAN	NAN	NAN	NAN	18.95	19.56	NAN	NAN	NAN	NAN
GLIS3	Q8NEA6	5	NAN	NAN	NAN	NAN	20.60	NAN	20.37	20.14	NAN	NAN
GLRX3	O76003	6	NAN	NAN	NAN	21.04	20.52	20.78	20.88	20.87	20.09	20.48
GLUL	P15104	15	22.84	24.23	20.00	19.89	19.10	19.62	20.62	26.42	NAN	NAN
GMPS	P49915	19	20.80	21.82	NAN	21.40	22.82	22.73	22.34	21.86	22.01	22.29
GNB2	P62879	5	20.48	NAN	NAN	NAN	20.21	20.60	20.15	20.35	20.65	20.66
GNL3L	Q9NVN8	12	NAN	NAN	NAN	NAN	22.32	23.01	21.17	20.37	NAN	NAN
GOLGA2	Q08379	18	NAN	NAN	21.89	22.41	21.39	21.75	22.80	21.90	21.08	21.68
GPANK1	O95872	11	NAN	NAN	NAN	NAN	23.24	22.52	20.82	20.56	NAN	NAN
GPATCH2L	Q9NWQ4	4	NAN	NAN	NAN	NAN	19.37	19.43	NAN	NAN	NAN	NAN
GPATCH4	Q5T3I0	4	NAN	NAN	NAN	NAN	18.52	18.36	NAN	NAN	NAN	NAN
GPS2	Q13227	4	NAN	NAN	NAN	NAN	19.67	20.08	19.45	19.44	NAN	NAN
GPSM1	Q86YR5	11	NAN	NAN	NAN	NAN	21.37	21.71	20.37	20.81	20.55	NAN
GRB2	P62993	10	NAN	NAN	23.35	23.52	23.47	23.79	23.28	23.32	22.36	22.69
GRWD1	Q9BQ67	14	NAN	NAN	21.92	23.01	24.14	24.79	23.05	23.19	20.48	22.39
GSC	P56915	4	NAN	NAN	NAN	20.64	21.12	21.25	NAN	20.58	NAN	NAN
GSDMA	Q96QA5	13	21.32	20.71	22.21	21.48	20.53	19.52	21.92	24.59	23.14	21.72
GSE1	Q14687	39	NAN	NAN	23.99	24.86	25.42	25.58	24.92	24.24	21.50	22.68
GSTM3	P21266	6	NAN	NAN	NAN	NAN	NAN	NAN	20.45	20.85	22.84	22.60
GSTP1	P09211	13	22.63	NAN	23.25	22.56	22.48	23.23	22.54	25.33	22.83	22.64
GTF2B	Q00403	8	NAN	NAN	NAN	21.81	21.93	22.78	21.95	22.05	21.21	21.79
GTF2E1	P29083	6	NAN	NAN	NAN	NAN	20.04	20.56	19.94	19.24	NAN	NAN
GTF2E2	P29084	6	NAN	NAN	NAN	NAN	19.65	19.91	19.32	NAN	NAN	NAN
GTF2F1	P35269	10	NAN	NAN	20.73	21.65	21.71	21.85	21.30	21.03	21.78	21.92
GTF2F2	P13984	5	NAN	NAN	NAN	21.77	21.16	20.99	21.68	20.90	NAN	21.35
GTF2H1	P32780	5	NAN	NAN	NAN	NAN	20.63	20.33	20.79	20.40	NAN	NAN
GTF2H2C	Q6P1K8	6	NAN	NAN	NAN	20.83	20.87	20.38	20.93	20.43	20.76	20.13
GTF2H3	Q13889	4	NAN	NAN	NAN	NAN	20.39	20.36	20.47	NAN	NAN	NAN
GTF2H4	Q92759	3	NAN	NAN	NAN	NAN	NAN	19.70	18.43	18.34	NAN	NAN
GTF2I	P78347	29	25.19	24.29	23.19	24.00	23.59	23.74	23.98	23.30	23.49	23.96
GTF3C1	Q12789	24	21.55	21.62	NAN	21.32	20.96	21.30	22.29	21.16	21.40	21.12
GTF3C3	Q9Y5Q9	16	20.63	20.85	NAN	21.04	20.53	20.49	21.50	20.55	NAN	20.35
GTF3C4	Q9UKN8	16	20.59	NAN	NAN	NAN	21.46	21.68	22.23	20.88	NAN	21.29
GTF3C5	Q9Y5Q8	8	NAN	NAN	NAN	20.26	20.14	20.46	20.95	20.15	20.40	20.62
GTPBP4	Q9BZE4	9	NAN	21.63	NAN	21.21	21.35	21.79	21.35	20.17	21.00	20.90
H1F0	P07305	5	21.50	22.13	23.20	24.56	22.13	22.27	23.66	23.81	25.01	25.13
H1FX	Q92522	5	22.21	21.09	21.11	22.19	20.71	20.50	22.11	21.74	22.76	22.64
H2AFV	Q71UI9	4	25.11	24.45	24.56	25.60	23.61	24.59	24.89	24.90	24.04	25.21
H2AFX	P16104	5	28.80	28.46	28.67	29.71	29.85	29.54	25.10	29.79	31.04	31.10
H2AFY	O75367	16	22.51	24.19	25.36	26.14	26.41	26.34	26.40	25.70	26.37	26.55
H2AFY2	Q9P0M6	12	NAN	NAN	21.96	23.30	23.07	22.91	23.77	22.66	23.78	23.95
H3F3B	P84243	4	22.96	21.85	23.46	24.34	25.81	25.78	26.39	25.35	25.29	25.53
HACD3	Q9P035	2	NAN	NAN	NAN	NAN	18.21	NAN	19.98	19.78	20.82	20.99
HAT1	O14929	10	NAN	NAN	20.85	21.54	21.20	21.42	22.08	21.63	21.28	21.39
HDAC1	Q13547	15	21.65	NAN	NAN	22.42	23.53	23.92	23.06	22.77	21.97	22.00
HDAC2	Q92769	18	25.41	24.23	23.24	24.99	25.16	25.24	24.69	24.26	23.76	23.78
HDAC3	O15379	10	NAN	NAN	NAN	NAN	21.71	21.43	21.09	21.38	NAN	20.43
HDAC4	P56524	5	NAN	NAN	NAN	NAN	19.61	20.04	19.63	NAN	NAN	NAN
HDAC7	Q8WUI4	9	NAN	NAN	NAN	NAN	21.02	21.45	20.72	21.34	NAN	19.89
HDGF	P51858	12	22.49	NAN	NAN	22.91	22.25	22.39	22.58	22.05	22.18	22.77
HDGFRP3	Q9Y3E1	4	20.36	NAN	NAN	NAN	20.19	NAN	21.02	20.73	NAN	21.04
HDLBP	Q00341	14	NAN	NAN	NAN	NAN	NAN	NAN	20.97	20.78	21.36	21.03
HDX	Q7Z353	7	NAN	NAN	NAN	NAN	21.49	21.39	20.85	NAN	NAN	NAN
HEATR3	Q7Z4Q2	3	NAN	NAN	NAN	NAN	NAN	NAN	19.49	18.28	NAN	NAN
HELLS	Q9NRZ9	6	21.15	20.98	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
HES7	Q9BYE0	3	NAN	NAN	NAN	NAN	NAN	19.80	20.11	20.20	NAN	NAN
HIC1	Q14526	7	NAN	NAN	NAN	NAN	20.43	20.57	20.37	20.08	NAN	NAN
HIKESHI	Q53FT3	3	NAN	NAN	NAN	NAN	20.82	20.90	NAN	19.25	NAN	NAN
HINT1	P49773	3	NAN	NAN	NAN	NAN	22.07	21.55	21.71	21.72	NAN	21.38
HIPK1	Q86Z02	16	NAN	NAN	NAN	NAN	23.68	23.91	22.24	22.58	NAN	NAN
HIPK2	Q9H2X6	18	NAN	NAN	NAN	NAN	23.84	23.56	20.97	20.32	NAN	NAN
HIST1H1A	Q02539	5	NAN	NAN	NAN	21.78	20.29	20.34	20.86	NAN	21.94	21.59
HIST1H1B	P16401	6	26.61	26.54	26.85	27.97	25.46	25.64	26.89	26.07	27.32	27.65
HIST1H1C	P16403	10	27.22	26.95	26.79	28.48	25.37	23.40	27.11	24.72	27.90	27.83
HIST1H1D	P16402	9	23.66	23.12	22.29	23.62	22.03	21.57	22.88	22.76	23.73	23.80

HIST1H2BF	P62807	10	30.72	29.72	30.59	31.30	31.00	31.08	31.42	31.13	31.48	32.32
HIST1H2BJ	P06899	10	NAN	NAN	27.03	28.41	24.60	23.12	26.45	26.41	26.59	27.50
HIST1H3A	P68431	5	NAN	26.07	26.16	25.24	26.07	26.37	27.37	26.30	25.83	26.48
HIST1H4H	P62805	12	30.52	29.79	30.77	31.99	30.65	30.94	31.43	31.30	31.74	32.33
HIST2H2AC	Q16777	4	20.41	27.64	29.01	25.67	26.72	27.72	28.99	27.75	29.17	28.28
HLTF	Q14527	39	20.16	NAN	23.26	23.76	24.35	24.71	23.68	23.93	23.31	24.17
HLX	Q14774	3	NAN	NAN	NAN	NAN	20.31	19.91	19.37	19.29	NAN	NAN
HMBS	P08397	2	NAN	NAN	NAN	NAN	18.28	18.73	18.16	18.19	NAN	NAN
HMCES	Q96FZ2	7	NAN	NAN	NAN	NAN	20.61	20.63	NAN	20.53	NAN	NAN
HMG20A	Q9NP66	9	NAN	20.96	NAN	21.39	23.51	23.88	22.94	22.49	20.32	21.20
HMG20B	Q9P0W2	15	NAN	NAN	21.74	23.45	22.69	23.12	23.30	23.39	21.54	22.43
HMGA1	P17096	5	23.52	23.84	23.54	24.82	23.21	23.05	23.73	23.37	24.31	24.23
HMGA2	P52926	3	21.13	20.94	NAN	19.92	NAN	19.17	19.40	19.53	20.36	19.71
HMGB1	P09429	7	24.46	24.20	24.57	25.19	23.61	23.54	24.49	23.87	24.16	24.36
HMGB2	P26583	4	23.67	NAN	NAN	NAN	22.33	21.92	23.32	22.58	22.93	23.00
HMGB3	O15347	4	22.72	NAN	NAN	NAN	21.43	21.12	22.32	21.11	21.46	NAN
HMGN1	P05114	5	23.52	20.93	20.37	21.69	21.62	21.71	22.89	22.31	23.76	23.29
HMGN3	Q15651	3	20.31	NAN	NAN	NAN	19.38	20.04	NAN	20.19	NAN	20.59
HNRNPA0	Q13151	11	24.23	25.30	24.59	24.83	26.44	26.99	25.58	25.88	24.55	24.46
HNRNPA2B1	P22626	24	28.40	28.86	27.16	28.05	28.27	28.44	28.60	28.21	27.98	27.97
HNRNPA3	P51991	15	25.95	26.58	25.00	25.77	25.72	25.89	25.80	25.52	25.42	25.56
HNRNPAB	Q99729	10	24.26	24.75	23.24	23.81	23.49	23.12	24.12	22.86	23.16	23.20
HNRNPC	P07910	20	27.38	27.76	24.83	25.92	24.72	24.48	26.40	24.92	26.14	25.91
HNRNPDL	O14979	9	23.29	24.12	22.51	23.97	24.50	24.56	24.18	23.64	23.85	23.92
HNRNPH1	P31943	19	26.86	27.56	26.26	26.89	27.56	27.80	27.38	27.36	26.99	26.83
HNRNPH2	P55795	16	22.03	21.72	21.77	22.29	23.72	23.91	23.47	23.44	23.52	23.18
HNRNPH3	P31942	11	24.32	24.58	22.60	22.87	24.70	24.86	24.46	24.26	23.79	23.92
HNRNPK	P14866	26	27.89	28.91	27.13	27.71	27.06	27.03	27.20	26.58	26.73	26.77
HNRNPLL	Q8WVV9	15	20.72	NAN	NAN	22.13	22.32	22.66	22.10	22.08	21.71	22.45
HNRNPM	P52272	36	27.09	27.41	26.05	26.95	27.18	27.57	27.82	27.30	27.11	27.11
HNRNPR	O43390	20	23.49	24.33	NAN	22.06	22.59	22.77	23.57	22.82	23.17	23.16
HNRNPU	Q00839	27	26.68	27.13	25.52	26.25	26.11	26.21	26.45	25.89	26.01	26.27
HNRNPUL1	Q9BUJ2	28	23.83	24.29	25.35	25.67	27.32	27.48	25.99	26.19	24.48	25.04
HNRNPUL2	Q1KMD3	16	21.75	22.04	21.41	22.74	22.85	23.06	23.40	22.91	23.25	23.00
HNRPA1	P09651	21	28.10	28.72	26.95	27.82	27.93	27.99	28.03	27.71	27.22	27.36
HNRPD	Q14103	11	24.91	25.67	22.37	23.60	24.68	24.52	24.93	23.98	24.25	24.21
HNRPF	P52597	15	24.95	25.60	24.83	24.88	26.08	26.09	25.97	25.57	24.99	24.48
HNRPK	P61978	26	21.54	21.09	NAN	NAN	21.62	22.40	22.80	21.07	22.47	NAN
HOMEZ	Q8IX15	5	NAN	NAN	20.76	NAN	20.13	19.92	19.58	19.14	NAN	19.93
HOXA10	P31260	11	NAN	NAN	NAN	NAN	22.66	22.85	22.24	22.13	NAN	NAN
HOXA11	P31270	7	NAN	NAN	NAN	NAN	23.28	23.59	NAN	NAN	NAN	NAN
HOXA9	P31269	6	NAN	NAN	NAN	NAN	21.37	21.42	NAN	NAN	NAN	NAN
HOXB4	P17483	8	NAN	NAN	NAN	21.00	23.06	23.31	21.66	21.17	NAN	NAN
HOXB5	P09067	4	NAN	NAN	NAN	NAN	20.31	20.05	NAN	20.21	NAN	NAN
HOXB6	P17509	7	NAN	NAN	NAN	NAN	22.03	22.19	21.16	21.19	NAN	NAN
HOXB7	P09629	7	NAN	NAN	NAN	NAN	23.69	24.06	21.69	21.52	NAN	20.13
HOXC10	Q9NYD6	12	NAN	NAN	20.55	21.70	23.43	22.65	21.75	21.73	NAN	20.37
HOXC11	O43248	10	NAN	NAN	NAN	22.34	21.38	21.78	21.86	21.60	NAN	21.30
HOXC5	Q00444	7	NAN	NAN	NAN	NAN	22.04	22.17	21.63	21.77	NAN	NAN
HOXC6	P09630	12	NAN	NAN	NAN	22.59	25.59	25.27	22.81	22.67	NAN	NAN
HOXC8	P31273	11	NAN	NAN	20.65	21.76	23.74	24.40	22.20	22.13	20.69	21.09
HOXC9	P31274	12	NAN	NAN	22.58	23.67	24.77	25.09	23.46	23.75	NAN	21.89
HOXD3	P31249	3	NAN	NAN	NAN	NAN	21.09	20.39	20.23	19.99	NAN	NAN
HOXD9	P28356	10	NAN	NAN	NAN	NAN	22.06	22.19	21.12	20.92	NAN	NAN
HP1BP3	Q5SSJ5	19	20.08	NAN	23.81	25.82	23.17	24.00	25.42	24.55	25.84	26.51
HSD17B12	Q53GQ0	2	NAN	NAN	NAN	NAN	NAN	NAN	18.65	19.55	NAN	NAN
HSP90AA1	P07900	23	22.88	22.45	22.15	23.26	24.04	24.02	23.21	24.07	22.81	23.13
HSP90AB1	P08238	25	25.55	25.40	23.58	24.89	25.40	25.72	25.40	25.91	24.94	25.34
HSP90B1	P14625	6	NAN	NAN	NAN	NAN	20.54	20.20	19.72	19.91	NAN	NAN
HSPA1A	P0DMV8	38	22.69	22.33	27.02	28.15	30.65	31.22	27.86	28.66	26.63	27.35
HSPA2	P54652	22	NAN	NAN	21.36	21.79	22.75	23.38	22.72	22.69	21.99	21.88
HSPA4	P34932	13	20.90	NAN	NAN	NAN	20.89	20.48	20.35	21.28	NAN	20.09
HSPA5	P11021	22	NAN	20.98	23.11	21.21	20.49	20.90	21.35	25.25	22.74	22.74
HSPA8	P11142	38	25.66	25.32	27.75	28.57	30.56	30.69	28.70	28.83	27.03	27.99
HSPB1	P04792	17	22.06	21.35	27.59	27.29	26.91	27.56	27.28	27.29	27.36	27.53
HSPB6	O14558	9	NAN	NAN	24.20	25.43	24.09	24.26	23.81	24.02	23.62	23.79
HSPC148	Q9P013	2	NAN	NAN	NAN	NAN	NAN	18.23	18.86	NAN	18.45	18.41
HSPC152	Q9UI30	5	NAN	20.28	NAN	20.77	22.66	23.19	21.70	22.29	20.96	NAN
HSPG2	P98160	19	NAN	NAN	NAN	20.82	19.96	20.46	19.96	19.67	20.89	23.17
HSPH1	Q92598	8	NAN	NAN	NAN	NAN	20.77	20.67	20.88	20.37	NAN	20.82

IDE	P14735	31	NAN	NAN	18.94	NAN	NAN	NAN	16.92	26.01	NAN	17.05
IGBP1	P78318	4	NAN	NAN	NAN	NAN	19.51	19.88	19.26	18.93	NAN	NAN
IGF2BP1	Q9NZI8	12	23.89	24.56	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
ILF2	Q12905	11	23.21	24.14	22.88	22.96	22.40	22.45	22.81	22.97	23.12	23.10
ILF3	Q12906	21	24.22	25.02	22.55	23.36	22.55	22.45	23.68	22.64	23.69	23.48
ILKAP	Q9H0C8	5	NAN	NAN	NAN	NAN	NAN	NAN	19.58	19.11	NAN	NAN
IMPDH2	P12268	4	NAN	NAN	NAN	NAN	NAN	19.26	20.03	20.24	20.13	NAN
INCENP	Q9NQS7	14	22.40	NAN	NAN	NAN	20.80	20.33	22.00	21.66	NAN	21.05
INTS10	Q9NVR2	20	NAN	NAN	20.23	20.69	23.44	23.63	22.99	21.89	20.07	21.30
INTS13	Q9NVM9	11	NAN	NAN	NAN	22.23	21.42	21.53	21.66	21.55	20.56	20.97
INTS14	Q96SY0	9	NAN	NAN	NAN	NAN	21.45	21.07	21.15	20.19	NAN	19.62
INTS4	Q96HW7	9	NAN	NAN	NAN	NAN	20.72	20.29	20.29	20.45	NAN	NAN
INTS5	Q6P9B9	14	NAN	NAN	NAN	NAN	23.50	22.63	21.51	21.24	NAN	20.07
INTS8	Q75QN2	7	NAN	NAN	NAN	NAN	20.16	20.90	20.31	20.12	NAN	NAN
INTS9	Q9NV88	6	NAN	NAN	NAN	NAN	20.08	20.67	20.45	19.78	NAN	NAN
IPO11	Q9UI26	16	NAN	20.83	21.44	22.12	21.42	22.49	21.76	21.08	20.13	20.19
IPO13	O94829	6	NAN	NAN	NAN	NAN	20.68	20.22	19.60	19.57	NAN	19.19
IPO7	O95373	18	NAN	NAN	23.70	23.07	22.30	22.15	22.38	22.00	23.04	22.93
IPO8	O15397	14	21.17	NAN	NAN	NAN	21.88	22.44	21.81	21.10	20.75	NAN
IPO9	Q96P70	6	NAN	NAN	NAN	NAN	19.94	19.72	NAN	19.64	NAN	NAN
IRF2BP1	Q8IU81	20	NAN	NAN	21.75	23.66	23.20	23.13	23.85	23.48	22.64	22.50
IRF2BP2	Q7Z5L9	11	20.39	NAN	NAN	21.08	21.08	20.93	22.17	21.05	NAN	19.97
IRF2BPL	Q9H1B7	7	NAN	NAN	NAN	NAN	NAN	NAN	18.86	18.57	NAN	NAN
IRF9	Q00978	6	NAN	NAN	NAN	NAN	21.06	21.00	20.88	NAN	NAN	NAN
IRX2	Q9BZI1	8	NAN	NAN	NAN	NAN	21.18	21.24	21.21	21.29	NAN	NAN
IRX5	P78411	11	NAN	NAN	NAN	NAN	22.18	22.26	22.32	23.04	NAN	21.78
ISG15	P05161	6	NAN	NAN	22.92	22.20	22.80	23.10	22.95	22.93	23.77	23.27
ITCH	Q96J02	6	NAN	NAN	NAN	NAN	20.70	21.17	NAN	NAN	NAN	NAN
IWS1	Q96ST2	3	NAN	NAN	NAN	NAN	19.49	19.62	NAN	19.47	NAN	NAN
JMJD1C	Q15652	15	20.37	19.67	NAN	19.65	21.74	22.55	20.66	20.09	NAN	NAN
JUN	P05412	4	NAN	NAN	NAN	NAN	22.28	22.35	20.84	20.43	NAN	20.94
JUNB	P17275	13	NAN	NAN	24.24	24.67	26.39	26.47	25.02	24.81	23.57	23.86
JUND	P17535	7	NAN	NAN	NAN	NAN	22.70	23.02	22.02	21.90	NAN	21.06
KAT2A	Q92830	3	NAN	NAN	NAN	NAN	19.77	19.69	NAN	NAN	NAN	NAN
KAT7	O95251	7	NAN	NAN	NAN	NAN	21.35	20.73	20.49	20.41	NAN	20.94
KCTD5	Q9NXV2	5	NAN	NAN	NAN	NAN	19.61	20.09	20.07	20.49	NAN	NAN
KDM1A	O60341	31	24.11	23.43	23.14	24.43	24.82	24.73	24.79	24.39	22.43	23.64
KDM2A	Q9Y2K7	10	NAN	NAN	20.66	20.31	21.28	21.33	21.67	21.13	21.48	21.34
KDM2B	Q8NHM5	8	NAN	NAN	NAN	NAN	20.34	20.32	20.28	20.30	NAN	NAN
KDM3B	Q7LBC6	5	NAN	NAN	NAN	NAN	18.94	19.76	19.64	19.04	NAN	18.81
KDM4A	O75164	5	NAN	NAN	NAN	NAN	20.07	20.77	19.61	NAN	NAN	NAN
KDM4B	O94953	19	NAN	NAN	21.38	21.97	21.77	22.83	21.10	20.94	NAN	21.05
KDM5B	Q9UGL1	10	NAN	NAN	NAN	NAN	19.91	19.63	20.10	19.17	19.96	19.70
KDM6B	O15054	22	NAN	NAN	NAN	NAN	23.41	24.03	21.37	21.01	NAN	NAN
KHDC4	Q7Z7F0	4	NAN	NAN	NAN	NAN	20.83	19.88	21.09	21.05	19.81	NAN
KHDRBS1	Q07666	8	24.30	24.93	24.90	25.30	25.24	25.46	24.38	24.71	24.01	24.51
KHDRBS3	O75525	3	NAN	NAN	NAN	NAN	19.56	19.45	20.04	19.36	NAN	NAN
KHSRP	Q92945	34	25.56	26.07	26.45	26.60	26.60	26.34	26.82	26.87	25.32	25.55
KIAA1958	Q8N8K9	2	NAN	NAN	NAN	NAN	18.17	18.48	NAN	NAN	NAN	NAN
KIF20A	O95235	24	23.45	23.22	NAN	22.05	22.81	23.20	24.34	24.00	23.61	22.60
KIF22	Q14807	12	22.20	22.53	21.62	22.50	22.22	22.17	22.72	22.08	21.25	21.80
KIF23	Q02241	7	NAN	NAN	NAN	NAN	20.01	NAN	20.78	20.52	NAN	NAN
KIF4A	O95239	24	21.20	NAN	NAN	21.09	21.26	20.91	22.86	21.41	19.79	20.19
KIFC1	Q9BW19	8	NAN	NAN	NAN	NAN	NAN	19.28	19.77	20.13	NAN	19.49
KLF16	Q9BXK1	5	NAN	NAN	NAN	NAN	21.92	22.04	21.50	22.02	NAN	21.67
KLF4	O43474	19	NAN	NAN	29.00	29.08	29.56	29.75	28.98	29.54	28.82	28.95
KLHL21	Q9UJP4	7	NAN	NAN	NAN	NAN	20.14	21.08	19.58	19.39	NAN	NAN
KPNA1	P52294	14	NAN	NAN	NAN	NAN	22.51	22.62	22.65	22.56	22.87	22.72
KPNA2	P52292	18	22.48	23.29	23.94	23.58	23.73	23.76	24.12	23.40	23.39	23.40
KPNA3	O00505	13	NAN	NAN	21.97	22.67	23.32	23.47	23.12	22.76	22.64	22.60
KPNA4	O00629	10	NAN	NAN	NAN	NAN	21.42	21.50	22.14	21.84	22.17	22.49
KPNA6	O60684	16	NAN	NAN	22.40	23.40	25.32	25.31	24.95	24.47	24.68	24.83
KPNB1	Q14974	15	NAN	NAN	22.62	21.66	21.62	21.55	22.77	22.17	22.83	23.10
KRT18	P05783	12	22.27	22.39	NAN	NAN	21.15	21.28	19.85	NAN	NAN	NAN
L1TD1	Q5T7N2	11	22.97	22.96	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
LAMP1	P11279	5	NAN	NAN	NAN	NAN	NAN	NAN	NAN	22.12	20.06	19.80
LANCL1	O43813	12	NAN	NAN	NAN	21.98	22.76	22.94	22.17	22.54	22.45	22.12
LANCL2	Q9NS86	4	NAN	NAN	NAN	NAN	19.89	19.18	NAN	19.45	NAN	NAN
LASP1	Q14847	14	20.82	20.74	23.26	24.50	24.75	23.83	24.55	23.75	24.06	23.98
LDB1	Q86U70	12	NAN	21.76	23.13	23.32	24.24	25.13	23.78	23.80	21.99	22.48

LENG1	Q96BZ8	5	NAN	NAN	NAN	NAN	20.43	20.33	19.37	NAN	NAN	NAN
LENG8	Q96PV6	22	NAN	NAN	NAN	19.71	24.04	24.12	21.74	21.69	NAN	NAN
LGALS3	P17931	5	NAN	NAN	22.56	20.73	22.81	23.30	22.58	22.70	21.73	22.47
LIG3	P49916	8	NAN	NAN	NAN	NAN	19.93	19.98	19.81	20.14	NAN	NAN
LIN28A	Q6UXM1	6	23.62	23.92	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
LMCD1	Q9NZU5	8	NAN	NAN	NAN	NAN	20.62	20.48	20.26	19.92	NAN	20.36
LMNB1	P20700	46	24.59	23.64	25.56	27.01	25.70	25.44	27.84	26.71	28.54	28.45
LMNB2	Q03252	43	21.46	21.01	25.87	27.57	25.71	25.49	28.04	26.65	28.91	28.80
LMO4	P61968	7	NAN	NAN	NAN	NAN	20.89	21.14	20.36	NAN	NAN	NAN
LPXN	O60711	4	NAN	NAN	NAN	NAN	NAN	18.99	19.82	19.58	20.29	NAN
LRIF1	Q5T3J3	12	NAN	NAN	NAN	21.79	22.00	21.70	21.55	21.50	21.25	20.97
LRRC41	Q15345	7	NAN	NAN	NAN	NAN	20.37	20.08	20.22	19.99	NAN	NAN
LRRC59	Q96AG4	10	NAN	NAN	22.23	21.58	21.04	20.32	22.16	21.40	22.76	23.13
LRWD1	Q9UFC0	11	NAN	21.73	NAN	NAN	22.43	22.52	21.70	20.88	21.51	NAN
LUC7L	Q9NQ29	9	NAN	NAN	NAN	NAN	19.75	19.39	20.78	19.55	NAN	19.41
LUC7L2	Q9Y383	9	21.26	21.55	21.04	22.22	21.62	21.41	22.95	21.73	22.56	22.62
LYPLA2	O95372	3	NAN	NAN	NAN	NAN	21.36	21.12	20.79	20.80	NAN	NAN
MAB21L1	Q13394	13	NAN	NAN	20.66	22.26	23.09	23.77	22.78	22.26	21.05	22.13
MAD1L1	Q9Y6D9	13	NAN	NAN	NAN	NAN	21.60	21.38	20.99	20.84	20.74	20.45
MAFF	Q9ULX9	6	NAN	NAN	23.08	23.82	23.65	24.01	23.69	23.92	22.01	22.94
MAFG	O15525	4	NAN	NAN	NAN	NAN	20.41	20.49	20.74	19.98	NAN	NAN
MAFK	O60675	5	NAN	NAN	NAN	NAN	20.92	20.73	21.32	20.86	NAN	20.35
MAGED1	Q9Y5V3	9	NAN	NAN	NAN	19.23	21.70	22.51	NAN	19.76	19.87	19.84
MAGED4	Q96JG8	7	NAN	NAN	NAN	NAN	19.78	19.38	NAN	18.80	NAN	NAN
MAGOHB	Q96A72	3	NAN	NAN	NAN	NAN	20.81	20.81	21.26	20.74	21.25	20.89
MAML1	Q92585	24	NAN	NAN	NAN	20.51	23.92	24.95	22.69	22.53	NAN	NAN
MAML2	Q8IZL2	10	NAN	NAN	NAN	NAN	21.45	22.12	NAN	20.05	NAN	NAN
MAMLD1	Q13495	7	NAN	NAN	NAN	NAN	21.57	21.65	20.26	20.73	NAN	NAN
MAP2K3	P46734	6	NAN	NAN	NAN	NAN	19.05	19.60	19.39	NAN	NAN	NAN
MAPK1	P28482	17	NAN	NAN	23.19	23.56	23.83	23.87	23.24	23.42	23.43	23.01
MAPK14	Q16539	8	NAN	NAN	NAN	NAN	21.55	21.62	21.04	21.32	NAN	NAN
MAPKAPK3	Q16644	2	NAN	NAN	NAN	NAN	19.15	19.25	NAN	NAN	NAN	NAN
MAPRE1	Q15691	6	NAN	NAN	NAN	NAN	20.58	20.84	21.16	20.51	20.86	20.58
MARCH1	Q9H992	12	NAN	NAN	NAN	NAN	21.81	21.65	NAN	NAN	NAN	NAN
MAT2A	P31153	4	20.37	NAN	NAN	NAN	20.24	19.98	20.19	19.63	20.32	19.99
MATR3	P43243	28	26.27	26.37	24.00	24.16	23.26	23.52	25.13	23.66	25.10	25.08
MAU2	Q9Y6X3	12	NAN	NAN	NAN	22.07	24.06	24.33	22.59	22.23	20.11	20.91
MAX	P61244	8	NAN	NAN	23.23	24.00	25.00	25.29	23.58	23.59	22.57	22.52
MAZ	P56270	8	NAN	NAN	NAN	NAN	20.01	20.21	20.25	19.90	NAN	NAN
MBD1	Q9UIS9	12	21.55	NAN	22.57	23.48	23.20	23.21	22.43	22.32	22.79	22.90
MBD2	Q9UBB5	7	NAN	NAN	NAN	21.66	21.30	22.18	21.50	20.96	NAN	21.99
MBD3	O95983	8	21.63	NAN	NAN	NAN	20.74	21.80	20.05	20.46	19.79	19.93
MBNL1	Q9NR56	12	NAN	NAN	25.66	23.51	23.63	23.85	23.88	23.93	22.76	22.90
MCM2	P49736	10	21.38	21.50	NAN	NAN	NAN	NAN	20.82	NAN	NAN	NAN
MCM3	P25205	16	21.87	22.36	NAN	NAN	20.38	20.43	22.01	20.66	21.09	21.35
MCM4	P33991	8	NAN	NAN	NAN	NAN	NAN	NAN	20.38	19.53	NAN	19.89
MCM6	Q14566	8	NAN	NAN	NAN	NAN	NAN	19.04	20.83	19.81	NAN	NAN
MCM7	P33993	25	23.51	23.17	21.75	21.79	23.22	22.82	23.75	22.90	22.24	21.98
MCMBP	Q9BTE3	16	NAN	NAN	22.15	22.17	21.66	21.71	21.42	21.01	NAN	NAN
MECP2	P51608	12	NAN	NAN	NAN	21.95	21.39	21.28	21.75	21.45	22.00	21.86
MED12	Q93074	39	NAN	NAN	NAN	19.85	24.51	23.99	20.92	20.80	NAN	18.18
MED14	O60244	7	NAN	NAN	NAN	NAN	20.99	20.36	18.76	19.32	NAN	NAN
MED15	Q96RN5	13	NAN	NAN	19.89	22.15	23.90	23.93	22.46	22.25	19.65	19.94
MED23	Q9ULK4	22	NAN	NAN	19.99	20.62	23.79	23.87	22.90	22.72	NAN	22.00
MED24	O75448	3	NAN	NAN	NAN	NAN	19.15	19.49	19.42	NAN	NAN	NAN
MEF2C	Q06413	6	NAN	NAN	NAN	21.19	21.86	21.92	21.67	20.71	NAN	NAN
MEF2D	Q14814	17	NAN	NAN	22.87	24.14	24.58	24.52	23.95	23.70	22.07	22.05
MEIS1	O00470	11	NAN	NAN	NAN	21.77	23.09	24.01	21.83	21.65	19.51	21.15
MEIS2	O14770	11	NAN	NAN	NAN	NAN	20.41	21.48	19.80	NAN	NAN	NAN
MEMO1	Q9Y316	8	NAN	NAN	20.52	NAN	21.16	21.69	21.04	20.88	20.23	20.45
MEN1	O00255	4	NAN	NAN	NAN	NAN	19.58	NAN	19.05	18.89	NAN	NAN
METTL3	Q86U44	8	NAN	NAN	NAN	NAN	20.02	20.23	20.26	20.03	NAN	NAN
MFSD10	Q14728	3	NAN	NAN	NAN	NAN	NAN	18.37	19.07	19.01	19.86	20.68
MGC4268	Q8IWI9	5	NAN	NAN	NAN	NAN	20.15	20.83	19.76	19.86	NAN	19.51
MGMT	P16455	6	NAN	NAN	NAN	NAN	20.77	20.65	20.08	19.44	NAN	19.58
MGST1	P10620	2	NAN	NAN	NAN	NAN	NAN	19.73	20.32	20.37	21.76	21.38
MIB2	Q96AX9	8	NAN	NAN	NAN	NAN	20.62	21.27	20.08	20.58	NAN	NAN
MIER1	P03971	7	NAN	NAN	NAN	NAN	20.22	20.77	20.46	20.17	NAN	NAN
MIIP	Q5JXC2	3	NAN	NAN	NAN	NAN	19.25	19.14	NAN	NAN	NAN	NAN
MKI67	P46013	15	21.03	NAN	NAN	NAN	18.76	19.18	20.59	19.39	20.63	20.40

MLF2	Q15773	11	NAN	NAN	22.83	23.30	26.67	27.79	23.80	24.68	22.98	23.65
MLL3	Q8NEZ4	5	NAN	NAN	NAN	NAN	19.04	19.21	NAN	19.35	NAN	NAN
MLLT1	Q03111	5	NAN	NAN	NAN	NAN	20.08	20.50	19.82	19.85	NAN	NAN
MN1	Q10571	4	NAN	NAN	NAN	NAN	NAN	NAN	18.89	18.98	NAN	NAN
MNAT1	P51948	6	NAN	NAN	NAN	NAN	19.83	20.10	20.96	19.19	NAN	20.06
MOCS3	O95396	3	NAN	NAN	NAN	NAN	19.44	19.67	19.46	18.99	NAN	NAN
MORC2	Q9Y6X9	8	NAN	NAN	NAN	NAN	19.52	20.05	19.08	19.40	NAN	NAN
MORC3	Q14149	19	NAN	NAN	NAN	NAN	21.96	22.50	22.64	21.79	20.28	21.28
MORF4L1	Q9UBU8	8	NAN	NAN	NAN	21.53	21.13	21.23	21.37	21.13	NAN	21.04
MORF4L2	Q15014	7	NAN	NAN	NAN	NAN	18.42	19.28	19.26	NAN	NAN	19.32
MPG	P29372	9	NAN	NAN	21.74	22.24	22.94	22.75	22.33	21.79	21.75	21.73
MRE11A	P49959	9	NAN	NAN	NAN	NAN	20.03	19.49	20.61	19.78	20.97	21.06
MRI1	Q9BV20	5	NAN	NAN	NAN	NAN	20.83	21.50	20.85	21.32	NAN	NAN
MRNIP	Q6NTE8	10	NAN	NAN	NAN	NAN	20.55	21.46	19.65	19.44	NAN	NAN
MRPL4	Q9BYD3	2	NAN	NAN	NAN	NAN	20.25	19.70	NAN	NAN	NAN	NAN
MRTO4	Q9UKD2	6	NAN	NAN	NAN	21.48	21.75	22.02	21.66	21.37	21.10	NAN
MSANTD4	Q8NCY6	7	NAN	NAN	NAN	NAN	22.54	21.81	NAN	20.65	20.18	NAN
MSH2	P43246	11	21.28	21.99	NAN	20.70	21.22	21.36	21.95	21.15	21.22	20.76
MSH6	P52701	25	23.87	22.29	21.59	22.43	22.80	23.66	23.82	22.22	22.50	22.54
MSN	P26038	8	NAN	NAN	NAN	NAN	20.23	NAN	20.83	21.04	21.59	21.69
MTA1	Q13330	21	23.48	23.14	21.63	22.89	23.22	23.53	23.37	22.28	20.49	21.81
MTA2	O94776	27	24.12	22.00	22.76	24.29	24.86	24.68	24.86	23.82	23.49	23.53
MTA3	Q9BTC8	17	21.60	NAN	NAN	NAN	21.34	20.64	20.97	20.82	20.61	20.34
MYC	P01106	18	NAN	NAN	26.63	27.06	27.46	27.96	25.33	25.30	27.27	26.79
MYL6	P60660	7	NAN	NAN	NAN	21.44	21.87	21.99	21.97	22.28	22.30	22.13
NAB2	Q15742	4	NAN	NAN	NAN	NAN	NAN	20.61	20.66	20.15	NAN	NAN
NACA	E9PAV3	3	NAN	NAN	NAN	NAN	18.76	18.47	NAN	22.34	NAN	NAN
NAGK	Q9UJ70	13	NAN	NAN	22.51	21.76	22.55	22.52	22.52	22.91	22.54	22.09
NAPA	P54920	7	NAN	NAN	NAN	NAN	19.93	19.97	20.93	20.79	NAN	20.74
NAT1	P18440	6	NAN	NAN	NAN	NAN	20.56	21.14	NAN	19.43	NAN	NAN
NCL	P19338	20	25.81	25.72	23.82	25.77	24.74	24.84	25.59	25.11	25.18	25.42
NCOA1	Q15788	9	NAN	NAN	NAN	NAN	21.00	20.92	20.64	20.58	NAN	NAN
NCOA2	Q15596	23	NAN	NAN	NAN	NAN	22.08	22.14	22.20	21.25	NAN	NAN
NCOA3	Q9Y6Q9	41	NAN	NAN	21.99	22.56	25.34	25.29	24.10	24.23	NAN	19.59
NCOR1	O75376	31	NAN	NAN	21.38	21.53	23.02	22.50	22.90	21.79	19.67	19.10
NCOR2	Q9Y618	76	20.29	NAN	24.91	25.03	26.28	25.90	25.17	25.82	23.28	24.07
NECAP2	Q9NVZ3	5	NAN	NAN	NAN	NAN	20.36	20.26	NAN	NAN	NAN	NAN
NEDD8	Q15843	2	NAN	NAN	NAN	NAN	19.72	NAN	NAN	NAN	20.10	20.56
NEIL2	Q969S2	9	NAN	NAN	NAN	NAN	22.40	22.65	21.66	21.39	NAN	20.47
NEK6	Q9HC98	8	NAN	NAN	NAN	NAN	21.47	21.12	NAN	NAN	NAN	NAN
NEK7	Q8TDX7	17	NAN	NAN	22.47	24.07	24.16	23.90	23.98	23.35	23.59	23.90
NFATC1	O95644	4	NAN	NAN	NAN	NAN	19.57	19.55	19.83	NAN	NAN	19.32
NFIC	P08651	23	NAN	NAN	24.91	24.78	25.98	26.60	24.74	24.64	23.98	23.68
NFIX	Q14938	21	NAN	NAN	25.01	25.65	26.67	26.89	25.86	25.52	24.36	24.49
NIFK	Q9BYG3	8	NAN	NAN	NAN	20.21	20.90	21.50	20.47	19.91	19.93	20.90
NIPBL	Q6KC79	30	NAN	NAN	NAN	21.05	24.04	23.69	22.54	21.77	NAN	19.57
NKRF	O15226	4	NAN	NAN	NAN	NAN	19.84	19.86	19.31	NAN	NAN	NAN
NKX2-6	A6NCS4	2	NAN	NAN	NAN	NAN	19.49	19.69	19.89	20.26	NAN	NAN
NLE1	Q9NVX2	7	NAN	NAN	NAN	NAN	21.23	21.39	20.71	20.21	NAN	20.53
NLK	Q9UBE8	3	NAN	NAN	NAN	NAN	NAN	19.16	18.41	17.67	NAN	NAN
NMD3	Q96D46	13	NAN	NAN	NAN	21.88	21.44	22.01	21.28	21.53	20.79	20.96
NME2	P22392	4	NAN	NAN	22.82	20.81	20.92	20.09	NAN	22.22	NAN	NAN
NNMT	P40261	11	NAN	NAN	21.85	22.69	21.81	21.87	22.41	21.74	22.98	22.43
NOC2L	Q9Y3T9	14	NAN	NAN	NAN	NAN	22.97	23.01	22.16	21.54	21.04	20.93
NOC4L	Q9BVI4	9	NAN	NAN	NAN	NAN	21.50	22.19	20.99	20.67	NAN	NAN
NOL6	Q9H6R4	15	NAN	20.07	22.33	21.24	22.16	23.24	21.86	21.62	21.59	21.21
NONO	Q15233	28	26.76	27.04	28.59	28.80	29.64	29.65	28.63	28.74	27.95	27.88
NOP16	Q9Y3C1	2	NAN	NAN	NAN	NAN	18.64	19.87	NAN	18.57	NAN	NAN
NOP58	Q9Y2X3	5	20.44	20.62	NAN	NAN	NAN	NAN	19.99	NAN	20.12	19.76
NOSIP	Q9Y314	14	NAN	NAN	23.03	23.78	24.55	24.76	24.19	24.28	22.77	23.36
NPLOC4	Q8TAT6	5	NAN	NAN	NAN	NAN	19.65	19.74	19.46	20.35	NAN	19.87
NPM1	P06748	9	25.63	25.27	23.10	22.89	24.10	23.61	24.55	24.49	24.92	24.82
NQO1	P15559	7	NAN	NAN	NAN	NAN	20.47	20.84	20.60	20.60	21.59	21.62
NR1B3	P13631	5	NAN	NAN	NAN	NAN	19.97	20.35	19.31	19.48	NAN	NAN
NR1D1	P20393	8	NAN	NAN	NAN	NAN	22.78	22.67	21.53	21.73	NAN	NAN
NR1H2	P55055	8	NAN	NAN	NAN	NAN	21.36	21.63	20.66	20.24	NAN	20.98
NR2B2	P28702	15	NAN	NAN	21.59	22.83	23.18	23.56	23.13	22.58	21.39	21.93
NR2C2	P49116	8	NAN	NAN	NAN	NAN	19.90	19.92	20.04	NAN	NAN	NAN
NR2F1	P10589	12	NAN	NAN	NAN	NAN	19.57	19.88	20.16	20.20	NAN	19.65
NR2F2	P24468	16	NAN	NAN	23.86	24.50	24.61	24.77	24.41	24.33	23.48	23.99

NR2F6	P10588	13	NAN	20.78	22.49	22.34	23.86	24.02	23.00	23.86	20.54	21.70
NR4A1	P22736	4	NAN	NAN	NAN	NAN	21.23	21.32	19.85	NAN	NAN	NAN
NR4A3	Q92570	11	NAN	NAN	NAN	NAN	21.58	22.19	21.48	21.68	NAN	NAN
NSMCE3	Q96MG7	4	NAN	NAN	NAN	NAN	19.19	19.07	NAN	NAN	NAN	NAN
NSUN2	Q08J23	29	20.26	19.83	21.94	23.66	23.94	24.10	24.38	23.96	23.91	24.09
NSUN5	Q96P11	11	NAN	NAN	NAN	NAN	21.75	21.70	21.06	21.20	NAN	NAN
NTHL1	P78549	7	NAN	NAN	NAN	NAN	20.87	20.73	NAN	NAN	NAN	NAN
NUCKS1	Q9H1E3	3	NAN	NAN	NAN	NAN	20.75	NAN	21.15	NAN	21.09	21.65
NUDT16L1	Q9BRJ7	9	NAN	NAN	21.12	20.84	22.62	23.40	22.03	22.09	21.15	20.94
NUDT21	O43809	9	21.69	23.47	22.27	23.30	23.18	23.38	23.03	22.84	21.99	21.95
NUFIP1	Q9UHK0	4	NAN	NAN	NAN	NAN	18.17	18.58	NAN	NAN	NAN	18.05
NUMA1	Q14980	58	22.69	22.20	24.63	26.08	26.57	26.64	26.40	25.98	24.84	25.38
NUP107	P57740	5	NAN	NAN	NAN	NAN	NAN	19.03	20.07	18.93	NAN	20.20
NUP133	Q8WUM0	12	NAN	NAN	NAN	NAN	NAN	NAN	20.85	19.53	21.14	21.57
NUP153	P49790	16	NAN	NAN	NAN	21.15	NAN	NAN	21.65	NAN	22.80	22.88
NUP155	O75694	4	NAN	NAN	NAN	NAN	19.11	19.51	20.04	19.18	NAN	19.64
NUP160	Q12769	7	NAN	NAN	NAN	NAN	18.38	NAN	20.27	18.70	NAN	20.52
NUP205	Q92621	14	NAN	NAN	NAN	NAN	20.92	20.13	20.37	NAN	NAN	NAN
NUP93	Q8N1F7	19	NAN	NAN	NAN	NAN	22.35	22.24	21.72	21.77	22.29	21.92
NUP98	P52948	11	NAN	NAN	NAN	NAN	NAN	NAN	21.44	20.35	22.09	21.34
NUTF2	P61970	3	NAN	NAN	NAN	NAN	19.21	19.37	NAN	NAN	NAN	19.37
NXF1	Q9UBU9	25	21.04	NAN	24.35	24.24	25.51	25.83	24.68	25.07	23.28	23.44
NXT1	Q9UKK6	2	NAN	NAN	NAN	NAN	19.85	20.37	NAN	NAN	NAN	NAN
OGT	O15294	31	NAN	NAN	23.06	24.04	24.68	24.46	24.45	24.01	23.33	23.46
ORC3	Q9UBD5	10	NAN	NAN	NAN	20.81	20.58	20.52	20.90	20.34	NAN	NAN
ORC4	O43929	5	NAN	NAN	NAN	NAN	20.21	20.56	NAN	19.84	NAN	NAN
ORC5	O43913	3	NAN	NAN	NAN	NAN	19.89	19.96	19.97	19.39	NAN	19.41
OSR1	Q8TAX0	4	NAN	NAN	NAN	NAN	21.98	22.07	20.88	21.04	NAN	NAN
OTUB1	Q96FW1	7	NAN	NAN	NAN	NAN	21.17	21.44	21.00	21.70	NAN	21.08
P15RS	Q96P16	7	NAN	NAN	NAN	20.77	20.77	21.29	21.52	21.04	21.29	20.93
P4HB	P07237	11	NAN	NAN	NAN	NAN	NAN	19.25	20.04	22.71	21.38	21.67
PA2G4	Q9UQ80	3	NAN	NAN	NAN	NAN	NAN	NAN	19.37	19.96	NAN	NAN
PABPC1	P11940	18	21.40	23.21	22.34	23.73	22.30	21.86	23.91	22.82	23.08	23.12
PABPN1	Q86U42	6	21.62	21.46	NAN	20.88	20.50	20.65	21.34	20.41	21.52	21.08
PAF1	Q8N7H5	6	NAN	NAN	NAN	19.83	19.64	19.24	19.83	NAN	20.03	20.42
PALLD	Q8WX93	5	NAN	NAN	NAN	NAN	NAN	NAN	19.98	19.62	19.86	NAN
PARP1	P09874	41	25.68	25.33	23.45	24.38	24.79	24.54	24.75	24.29	23.91	24.28
PATZ1	Q9HBE1	14	NAN	21.26	NAN	NAN	22.50	23.39	21.54	21.10	NAN	NAN
PAX3	P23760	13	NAN	NAN	19.86	21.01	24.51	24.11	22.02	22.29	20.87	21.21
Pax9	P55771	11	NAN	NAN	NAN	NAN	22.37	22.83	20.29	20.67	NAN	NAN
PAXIP1	Q6ZW49	9	NAN	NAN	NAN	NAN	20.91	20.91	20.43	20.78	NAN	NAN
PBEF1	P43490	11	NAN	NAN	NAN	NAN	20.61	20.50	21.84	22.56	NAN	NAN
PBRM1	Q86U86	6	NAN	NAN	NAN	NAN	20.24	20.36	20.69	20.01	19.96	NAN
PBX1	P40424	12	NAN	NAN	21.16	21.44	22.10	21.86	21.40	21.34	NAN	21.10
PBX2	P40425	12	NAN	NAN	NAN	NAN	22.61	23.14	21.68	21.40	NAN	20.47
PC4	P53999	7	23.55	22.51	NAN	23.67	23.87	23.73	24.12	23.61	24.03	24.05
PCBP1	Q15365	13	24.83	25.32	24.80	25.18	25.39	25.56	25.22	25.10	24.57	24.76
PCBP2	Q15366	12	23.85	24.88	23.91	24.07	23.67	23.75	23.94	23.80	23.54	23.55
PCBP4	P57723	5	NAN	NAN	NAN	NAN	19.57	20.34	18.81	NAN	NAN	NAN
PCF11	O94913	5	NAN	NAN	NAN	20.02	20.01	20.02	20.04	19.50	NAN	NAN
PCGF3	Q3KNV8	9	NAN	NAN	NAN	NAN	22.05	21.89	20.63	20.61	NAN	NAN
PCGF5	Q86SE9	5	NAN	NAN	NAN	NAN	20.54	20.76	NAN	NAN	NAN	NAN
PCID2	Q5JVF3	12	NAN	NAN	NAN	NAN	22.27	22.94	20.62	20.12	NAN	NAN
PCMT1	P22061	9	NAN	NAN	21.87	21.66	22.41	22.59	21.68	21.95	21.38	21.89
PCNA	P12004	5	21.74	21.49	NAN	NAN	20.89	20.85	21.55	20.95	21.07	20.80
PCYT1A	P49585	14	NAN	NAN	22.08	23.11	23.34	23.21	23.38	23.44	24.27	24.04
PDCD4	Q53EL6	4	NAN	NAN	NAN	NAN	20.47	20.34	20.47	20.36	NAN	20.33
PDCD5	O14737	4	NAN	NAN	NAN	NAN	21.29	21.05	20.84	20.65	20.36	21.19
PDCD6	O75340	10	NAN	NAN	23.75	23.75	25.56	25.41	24.53	24.44	22.34	22.47
PDIA3	P30101	10	NAN	NAN	NAN	21.25	NAN	20.55	21.14	22.23	22.35	21.80
PDIA6	Q15084	6	NAN	20.28	20.99	NAN	19.61	NAN	20.31	21.84	20.80	20.82
PDLIM1	O00151	3	NAN	NAN	NAN	NAN	19.03	18.71	19.74	NAN	NAN	19.17
PDLIM2	Q96JY6	8	NAN	NAN	NAN	22.29	21.56	22.06	21.39	22.48	20.83	21.26
PDLIM4	P50479	10	NAN	NAN	22.37	22.32	22.76	22.99	22.20	22.46	22.06	21.77
PDS5A	Q29RF7	11	20.10	21.65	NAN	NAN	20.74	20.65	21.42	20.70	20.80	20.74
PDS5B	Q9NTI5	14	NAN	20.81	21.30	22.44	21.27	21.91	22.14	21.47	20.38	20.98
PEA15	Q15121	3	NAN	NAN	NAN	NAN	19.10	19.55	19.84	19.97	22.07	20.92
PEBP1	P30086	9	22.55	23.61	23.49	22.29	22.71	22.85	22.52	24.58	22.82	22.97
PEF1	Q9UBV8	8	NAN	NAN	22.73	22.84	24.05	24.76	23.35	23.63	22.10	21.98
PELO	Q9BRX2	4	NAN	NAN	NAN	NAN	20.39	20.57	19.61	NAN	NAN	NAN

PES1	O00541	8	20.80	NAN	NAN	20.90	20.97	21.14	21.14	20.27	20.67	20.49
PFDN2	Q9UHV9	4	NAN	NAN	NAN	20.63	20.84	20.68	20.48	20.13	NAN	NAN
PFDN5	Q99471	2	NAN	NAN	NAN	NAN	19.10	19.49	NAN	NAN	NAN	NAN
PFKFB3	Q16875	8	NAN	NAN	NAN	NAN	NAN	20.34	21.08	21.36	21.02	21.13
PFN1	P07737	8	24.39	24.63	25.30	25.68	25.84	26.03	25.16	25.41	25.06	25.15
PFN2	P35080	6	NAN	NAN	NAN	20.90	21.18	NAN	20.51	20.40	NAN	20.56
PGAM1	P18669	7	22.17	NAN	NAN	NAN	20.98	20.57	20.17	22.74	20.31	NAN
PGD	P52209	5	NAN	NAN	NAN	NAN	19.36	19.06	19.11	21.30	NAN	19.54
PGK1	P00558	17	NAN	20.85	23.16	22.03	22.45	23.38	22.41	24.64	23.04	23.43
PHB2	Q99623	4	NAN	NAN	NAN	NAN	19.71	19.77	19.02	20.81	19.84	20.40
PHC2	Q8IXK0	6	NAN	NAN	NAN	21.02	21.26	21.03	21.07	20.10	NAN	20.52
PHF14	O94880	18	NAN	NAN	21.03	22.97	23.00	23.36	22.85	21.99	NAN	21.52
PHF5A	Q7RTV0	3	NAN	NAN	NAN	NAN	19.46	19.47	19.68	19.45	NAN	NAN
PHF6	Q8IWS0	6	21.34	NAN	NAN	NAN	20.31	20.05	20.42	20.60	20.81	20.88
PHF8	Q9UPP1	14	NAN	NAN	NAN	20.73	22.59	22.41	21.60	21.07	20.19	20.90
PHIP	Q8WWQ0	10	NAN	NAN	NAN	NAN	19.81	19.36	20.33	19.22	19.70	20.51
PHPT1	Q9NRX4	6	NAN	NAN	20.44	21.46	22.48	22.84	22.29	22.26	22.20	21.82
PIAS1	O75925	15	NAN	23.44	23.52	22.52	24.46	24.68	23.63	22.78	21.29	22.11
PIAS2	O75928	13	NAN	NAN	NAN	NAN	21.70	21.38	20.52	20.21	NAN	NAN
PIAS3	Q9Y6X2	15	NAN	NAN	NAN	NAN	23.95	24.71	22.58	22.12	20.82	21.12
PIAS4	Q8N2W9	17	20.12	20.78	22.72	22.48	24.87	24.90	23.58	22.93	20.52	21.08
PIN1	Q13526	7	NAN	NAN	22.38	23.13	23.55	23.76	22.94	23.17	22.16	22.18
PINX1	Q96BK5	5	NAN	NAN	NAN	NAN	20.19	19.93	NAN	NAN	NAN	NAN
PITPNB	P48739	6	NAN	NAN	NAN	NAN	20.87	20.46	20.17	20.22	20.88	20.34
PITX1	P78337	4	NAN	NAN	NAN	NAN	19.00	19.86	18.54	NAN	NAN	NAN
PITX2	Q99697	8	NAN	NAN	20.86	21.57	22.94	23.22	22.19	22.28	NAN	21.37
PKP1	Q13835	24	22.21	21.22	24.54	22.24	23.87	23.40	21.73	24.54	21.74	22.42
PLAA	Q9Y263	10	NAN	NAN	NAN	NAN	20.06	20.47	20.63	20.43	20.20	20.57
PLAGL2	Q9UPG8	2	NAN	NAN	NAN	NAN	17.90	19.09	17.40	NAN	NAN	NAN
PLEC	Q15149	91	NAN	21.46	22.95	22.67	21.97	22.38	24.09	25.49	24.48	24.54
PLK1	P53350	6	NAN	20.47	NAN	20.53	20.17	20.17	20.03	20.30	NAN	NAN
PLRG1	O43660	12	NAN	NAN	20.22	22.14	22.36	22.51	22.37	22.25	21.83	22.12
PML-RAR	O15305	20	NAN	NAN	NAN	NAN	NAN	NAN	21.46	21.70	22.14	21.93
PMM2	Q15126	4	NAN	NAN	20.10	NAN	20.87	20.70	20.20	NAN	NAN	NAN
PMVK	Q96T60	3	NAN	NAN	NAN	NAN	NAN	18.67	18.75	19.67	NAN	19.08
PNO1	P00491	7	NAN	NAN	NAN	NAN	22.38	22.59	21.53	21.19	NAN	19.92
PNP	P01298	11	20.79	NAN	22.89	20.53	21.16	21.21	20.82	22.20	20.50	21.07
POGZ	Q7Z3K3	16	21.20	21.61	NAN	21.30	21.68	20.91	21.66	21.10	20.70	20.71
POLD2	P49005	3	NAN	NAN	NAN	NAN	19.41	NAN	20.55	19.58	NAN	NAN
POLDIP3	Q9BY77	12	20.91	NAN	NAN	22.03	22.90	22.86	22.88	22.30	22.02	21.78
POLR1C	Q9Y253	5	NAN	NAN	NAN	NAN	20.22	19.87	19.61	19.68	NAN	19.90
POLR2A	P24928	9	20.45	NAN	NAN	19.44	20.25	20.57	20.64	19.68	NAN	20.13
POLR2B	P30876	18	21.14	NAN	NAN	21.91	21.67	21.31	21.77	20.81	20.67	21.26
POLR2E	P19388	4	NAN	20.23	NAN	20.24	20.07	20.06	20.08	19.88	20.40	20.27
POLR2H	P52434	4	NAN	NAN	NAN	NAN	20.97	21.36	21.28	21.22	21.62	21.44
POLR2I	P36954	4	NAN	NAN	NAN	NAN	20.70	20.85	NAN	NAN	NAN	NAN
POM121C	A8CG34	7	NAN	NAN	NAN	NAN	21.09	21.04	20.39	20.19	NAN	20.34
POU3F1	Q03052	7	NAN	NAN	NAN	NAN	19.53	NAN	19.58	21.35	21.16	20.29
POU5F1	Q01860	23	28.20	28.19	31.63	32.03	33.54	33.86	32.47	32.70	32.23	32.15
PPA1	Q15181	6	NAN	NAN	NAN	NAN	20.40	20.63	20.58	21.50	NAN	NAN
PPHLN1	Q8NEY8	5	20.23	19.65	NAN	19.94	19.40	18.93	19.29	19.12	NAN	NAN
PPIA	P62937	11	25.64	25.49	25.64	26.70	27.64	27.89	26.77	27.03	26.86	27.19
PPID	Q08752	3	NAN	NAN	NAN	NAN	19.19	18.98	18.50	NAN	NAN	NAN
PPIL1	Q9Y3C6	5	NAN	NAN	21.68	22.14	22.58	22.65	21.63	21.65	NAN	21.38
PPIL2	Q13356	17	NAN	NAN	NAN	19.68	23.05	24.01	21.58	21.49	NAN	19.49
PPIL3	Q9H2H8	5	NAN	NAN	NAN	NAN	20.94	21.85	NAN	21.16	NAN	NAN
PPIL4	Q8WUA2	9	NAN	NAN	NAN	NAN	21.18	21.03	21.04	20.90	20.83	21.18
PPM1G	O15355	9	NAN	NAN	NAN	NAN	20.94	20.70	21.06	20.54	21.27	21.21
PPP1CA	P62136	16	23.49	23.62	23.12	23.72	23.26	23.77	23.52	23.52	23.38	23.29
PPP1CB	P62140	12	NAN	NAN	NAN	NAN	NAN	NAN	20.07	20.99	NAN	NAN
PPP1CC	P36873	15	NAN	NAN	NAN	NAN	19.92	NAN	20.02	19.61	19.87	NAN
PPP1R8	Q12972	4	NAN	NAN	NAN	NAN	21.19	21.77	21.21	NAN	NAN	NAN
PPP2CB	P62714	7	NAN	NAN	NAN	NAN	19.29	19.69	19.89	21.23	19.95	19.45
PPP2R1A	P30153	8	NAN	NAN	20.88	NAN	20.30	20.94	21.07	21.08	20.79	21.52
PQBP1	O60828	5	NAN	NAN	NAN	NAN	20.87	20.75	20.78	20.89	NAN	NAN
PRCC	Q92733	5	NAN	NAN	NAN	NAN	19.80	19.36	19.77	19.29	NAN	NAN
PRDM1	O75626	4	NAN	NAN	NAN	NAN	19.73	20.09	NAN	NAN	NAN	NAN
PRDX2	P32119	10	NAN	23.24	24.67	NAN	22.48	NAN	21.50	23.32	22.98	21.79
PRDX4	Q13162	6	NAN	NAN	NAN	NAN	NAN	NAN	18.81	18.85	NAN	NAN
PRDX5	P30044	5	NAN	NAN	NAN	NAN	19.74	20.25	19.67	20.37	NAN	19.74

PRDX6	P30041	11	22.09	22.54	22.28	22.03	21.76	21.68	21.54	22.51	22.62	22.28
PRKDC	P78527	85	23.50	24.22	21.98	24.05	23.98	23.75	25.58	24.90	25.17	25.26
PRMT1	Q99873	13	23.41	23.48	23.48	24.19	24.73	24.90	24.81	24.54	24.56	24.70
PRPF19	Q9UMS4	11	NAN	21.04	22.03	23.69	23.06	23.09	23.69	23.34	23.55	23.59
PRPF3	O43395	7	NAN	NAN	NAN	NAN	20.13	19.93	20.03	19.78	19.73	19.92
PRPF31	Q8WWY3	9	20.51	NAN	NAN	21.81	21.35	21.18	21.38	20.99	20.30	20.83
PRPF4	O43172	16	NAN	NAN	22.68	22.51	22.62	22.78	22.83	22.63	22.13	22.13
PRPF6	O94906	28	NAN	NAN	20.61	23.63	23.21	23.80	23.62	23.54	22.49	22.14
PRPF8	Q6P2Q9	20	19.82	21.47	20.30	20.76	20.68	20.35	22.46	21.75	21.36	21.98
PRR12	Q9ULL5	20	NAN	NAN	NAN	20.19	22.22	22.89	21.50	21.39	NAN	NAN
PRRX1	P54821	10	NAN	NAN	NAN	21.72	22.64	23.07	22.48	21.64	21.85	21.88
PRRX2	Q99811	10	NAN	NAN	24.15	24.67	26.38	26.35	24.97	25.10	23.51	24.05
PSIP1	O75475	10	24.32	23.24	NAN	22.25	21.19	21.20	22.54	21.99	22.45	22.64
PSMA1	P25786	3	19.45	NAN	NAN	NAN	19.03	NAN	18.56	20.93	19.54	NAN
PSMA4	P25789	6	NAN	NAN	NAN	NAN	20.61	20.17	NAN	20.85	NAN	NAN
PSMA5	P28066	6	NAN	NAN	NAN	NAN	21.20	21.15	21.12	22.15	22.04	21.76
PSMA6	P60900	6	NAN	19.82	21.30	19.97	19.84	19.42	19.88	21.23	20.25	19.81
PSMA7	O14818	6	NAN	NAN	NAN	NAN	20.83	21.13	20.36	22.26	21.50	20.77
PSMB1	P20618	4	NAN	NAN	NAN	NAN	20.96	20.67	19.65	21.34	NAN	NAN
PSMB2	P49721	6	NAN	NAN	20.99	NAN	20.69	20.83	20.06	21.78	20.63	NAN
PSMB3	P49720	4	NAN	NAN	NAN	NAN	20.77	20.91	19.54	21.22	NAN	20.31
PSMB4	P28070	7	NAN	NAN	NAN	NAN	22.01	22.15	NAN	21.28	NAN	20.70
PSMB5	P28074	9	NAN	20.35	20.74	NAN	21.59	22.07	20.71	22.33	20.98	20.87
PSMC3	P17980	4	NAN	NAN	NAN	NAN	NAN	18.30	19.05	19.63	NAN	NAN
PSMD10	O75832	4	NAN	NAN	NAN	NAN	20.33	20.15	20.27	NAN	20.26	20.12
PSMD5	Q16401	4	NAN	NAN	20.51	NAN	19.61	19.56	NAN	NAN	NAN	NAN
PSMD9	O00233	8	NAN	NAN	21.36	21.86	22.40	22.26	22.53	21.81	22.09	22.03
PSME3	P61289	4	NAN	NAN	NAN	NAN	20.63	19.84	20.42	20.67	20.85	20.94
PSMF1	Q92530	4	NAN	NAN	NAN	NAN	22.14	22.32	21.65	21.03	21.48	20.98
PSPC1	Q8WXF1	24	24.33	25.10	26.55	25.81	26.74	26.97	26.12	25.90	24.62	25.10
PTBP1	P26599	20	25.19	26.56	25.64	26.05	26.45	26.56	26.69	26.52	25.72	25.91
PTGES3	Q15185	5	22.51	22.39	NAN	21.79	21.43	21.79	21.39	21.85	21.36	21.88
PTMA	P06454	4	21.57	21.33	NAN	NAN	20.04	20.05	20.40	19.48	NAN	20.35
PTOV1	Q86YD1	2	NAN	NAN	NAN	NAN	18.93	19.57	18.41	18.84	19.28	18.97
PTRHD1	Q6GMV3	3	NAN	NAN	NAN	NAN	21.09	21.31	20.09	20.53	19.58	19.48
PWP2	Q15269	6	NAN	NAN	NAN	NAN	19.77	20.18	19.13	18.94	NAN	NAN
PYCARD	Q9ULZ3	5	NAN	NAN	NAN	NAN	20.18	20.01	NAN	19.86	NAN	NAN
QKI	Q96PU8	11	NAN	NAN	NAN	NAN	22.58	22.50	22.46	21.89	NAN	21.94
QRICH1	Q2TAL8	7	NAN	NAN	NAN	NAN	20.71	20.24	20.30	20.47	NAN	20.59
QTRT2	Q9H974	3	NAN	NAN	NAN	NAN	19.93	20.21	NAN	19.37	NAN	NAN
RAB2	P61019	6	NAN	NAN	NAN	NAN	NAN	NAN	20.20	21.58	21.00	NAN
RAB5C	P51148	5	NAN	NAN	NAN	NAN	NAN	20.81	21.12	22.27	21.33	21.14
RAB6A	P20340	2	NAN	NAN	20.70	NAN	NAN	NAN	NAN	NAN	21.21	20.48
RAB7A	P51149	9	NAN	NAN	21.68	21.88	19.99	19.68	20.32	22.59	21.94	21.72
RACGAP1	Q9H0H5	5	NAN	NAN	NAN	NAN	19.79	NAN	20.09	19.19	NAN	NAN
RACK1	P63244	15	24.03	23.99	23.34	23.55	24.56	24.31	24.10	24.56	24.51	24.36
RAD21	O60216	11	NAN	NAN	NAN	NAN	21.33	21.44	21.45	NAN	NAN	NAN
RAD51C	O43502	4	NAN	NAN	NAN	NAN	19.00	19.57	18.85	NAN	NAN	NAN
RAD54L2	Q9Y4B4	32	NAN	NAN	NAN	NAN	24.26	24.25	23.13	22.86	NAN	NAN
RAE1	P78406	6	NAN	NAN	NAN	NAN	21.59	21.64	21.20	20.88	20.69	21.13
RAI1	Q7Z5J4	40	NAN	NAN	21.31	22.77	24.15	24.75	22.79	22.65	NAN	NAN
RALY	Q9UKM9	8	22.68	23.53	21.50	21.94	20.83	21.38	22.80	21.86	22.52	22.04
RAN	P62826	10	25.14	25.10	24.95	26.13	25.65	25.80	25.98	25.16	25.49	25.23
RANBP5	O00410	23	NAN	NAN	23.27	20.72	22.48	22.97	22.82	22.33	22.26	22.21
RAP1B	P61224	2	NAN	NAN	NAN	NAN	NAN	NAN	18.82	20.06	19.24	20.05
RAVER1	Q8IY67	24	20.27	22.96	24.07	24.31	25.63	25.63	25.08	24.80	22.72	23.07
RBBP4	Q09028	17	25.50	24.80	23.72	25.03	25.14	25.34	25.06	24.45	23.83	23.97
RBBP7	Q16576	16	22.54	21.59	NAN	23.33	22.87	23.41	23.18	22.78	21.77	22.15
RBFOX2	O43251	6	20.65	20.49	20.77	21.27	22.12	22.28	21.18	21.26	20.44	20.81
RBM10	P98175	8	NAN	NAN	NAN	NAN	20.66	20.54	20.88	20.40	20.56	20.24
RBM12	Q9NTZ6	8	NAN	NAN	NAN	22.70	21.88	22.07	22.55	22.38	22.15	22.24
RBM14	Q96PK6	34	25.45	26.42	27.89	28.29	29.89	30.75	28.92	29.27	26.21	26.81
RBM15	Q96T37	7	20.27	19.94	NAN	20.19	20.13	20.18	20.06	19.81	19.93	19.82
RBM22	Q9NW64	13	NAN	NAN	23.04	23.96	24.32	24.69	23.99	24.20	23.35	23.54
RBM23	Q86U06	5	NAN	NAN	NAN	NAN	23.55	23.32	NAN	23.24	NAN	NAN
RBM25	P49756	5	NAN	NAN	NAN	NAN	19.79	NAN	21.31	19.93	20.99	20.26
RBM27	Q9P2N5	20	NAN	20.75	22.54	23.28	24.14	24.37	23.53	23.56	22.06	22.47
RBM3	P98179	3	NAN	NAN	NAN	NAN	20.99	20.38	21.79	20.68	NAN	NAN
RBM33	Q96EV2	25	NAN	20.08	22.37	23.05	24.61	25.35	23.02	23.15	18.90	21.04
RBM39	Q14498	18	22.40	22.82	22.64	23.58	23.53	23.97	24.32	23.30	23.51	23.67

RBM4	Q9BWF3	19	24.47	24.71	23.89	25.22	26.57	26.55	25.69	25.68	23.93	23.82
RBM42	Q9BTD8	5	NAN	NAN	NAN	NAN	18.96	19.01	20.18	NAN	NAN	NAN
RBM4B	Q9BQ04	18	NAN	NAN	NAN	NAN	20.52	20.74	NAN	NAN	NAN	NAN
RBM6	P78332	8	NAN	NAN	NAN	NAN	20.02	20.10	19.55	19.48	NAN	NAN
RBM7	Q9Y580	9	NAN	NAN	NAN	NAN	21.71	22.25	21.29	20.17	NAN	NAN
RBM8	Q9Y5S9	4	NAN	NAN	NAN	21.84	21.16	21.19	21.62	20.93	NAN	21.52
RBMX	P38159	15	25.87	25.91	23.88	24.88	24.46	24.71	25.00	24.48	24.69	24.50
RBPJ	Q06330	14	22.25	22.14	21.39	23.08	22.99	23.70	23.27	23.10	22.35	22.81
RCC1	P18754	13	22.01	21.78	23.11	23.68	23.46	24.01	24.14	23.51	24.14	23.84
RCC2	Q9P258	23	26.20	25.74	23.62	24.78	25.53	25.77	25.31	24.78	24.13	24.36
RCOR1	Q9UKL0	12	NAN	NAN	22.04	23.00	23.45	23.48	23.45	23.04	22.07	22.09
RCOR3	Q9P2K3	6	NAN	NAN	NAN	NAN	19.18	18.86	18.83	NAN	NAN	NAN
RECQL	P46063	22	21.46	NAN	21.61	23.77	24.69	24.60	25.14	23.97	24.59	25.16
RERE	Q9P2R6	9	NAN	NAN	20.78	21.28	22.31	21.51	21.91	21.13	20.98	20.27
REXO1	Q8N1G1	7	NAN	NAN	NAN	NAN	19.81	19.87	NAN	NAN	NAN	NAN
REXO1L1P	Q8IX06	7	NAN	NAN	NAN	NAN	NAN	19.67	NAN	20.03	20.82	22.79
RFX1	P22670	10	NAN	NAN	NAN	21.08	21.35	21.38	21.20	21.08	20.23	NAN
RING1	Q06587	8	NAN	NAN	NAN	NAN	22.19	22.22	22.04	21.44	21.43	21.05
RLIM	Q9NVW2	3	NAN	NAN	NAN	NAN	18.83	19.39	NAN	NAN	NAN	NAN
RNASE7	Q9H1E1	4	NAN	NAN	NAN	NAN	18.53	NAN	18.67	24.25	NAN	19.03
RNF111	Q6ZNA4	7	NAN	NAN	NAN	NAN	21.14	21.80	19.93	NAN	NAN	NAN
RNF113A	O15541	8	NAN	NAN	NAN	NAN	21.48	21.10	21.12	20.76	20.78	20.65
RNF114	Q9Y508	8	NAN	20.55	NAN	NAN	22.35	22.56	21.48	21.65	21.38	19.92
RNF126	Q9BV68	4	NAN	NAN	NAN	20.93	20.88	21.05	20.75	20.79	NAN	NAN
RNF138	Q8WVD3	3	NAN	NAN	NAN	NAN	19.91	NAN	19.58	19.32	NAN	NAN
RNF2	Q99496	8	NAN	NAN	NAN	NAN	NAN	NAN	21.09	20.05	NAN	20.58
RNF20	Q5VTR2	19	NAN	20.10	NAN	22.54	21.64	21.58	23.09	21.79	21.43	22.16
RNF216	Q9NWF9	9	NAN	NAN	NAN	NAN	21.17	21.27	20.82	20.12	NAN	NAN
RNF4	P78317	4	NAN	NAN	NAN	NAN	20.28	20.53	NAN	NAN	NAN	NAN
RNF40	O75150	17	NAN	NAN	NAN	21.76	21.18	21.15	21.94	21.50	21.51	22.13
RNGTT	O60942	17	NAN	NAN	NAN	22.27	23.29	23.18	22.71	22.47	22.36	22.47
RNH1	O60930	22	19.65	21.70	25.90	26.10	25.33	25.44	25.71	25.88	25.36	26.09
RNMT	P13489	7	NAN	NAN	NAN	NAN	20.77	20.38	NAN	20.21	NAN	20.41
RPA1	Q15287	27	23.26	22.00	23.66	24.08	26.07	25.60	25.20	25.63	24.55	24.86
RPA2	P27694	6	NAN	NAN	NAN	NAN	21.84	21.90	21.91	21.23	NAN	21.02
RPA3	P15927	2	NAN	NAN	NAN	NAN	21.36	21.56	NAN	21.12	NAN	20.32
RPL10	P49247	6	21.17	21.70	NAN	20.61	20.15	20.16	20.91	20.44	21.25	21.81
RPL10A	P62906	6	NAN	NAN	NAN	NAN	20.63	21.38	21.41	20.37	NAN	21.62
RPL11	P62913	3	NAN	NAN	21.26	21.27	21.46	NAN	NAN	21.55	21.88	21.61
RPL12	P30050	6	NAN	22.29	21.60	21.79	22.07	21.64	21.73	21.92	21.98	22.21
RPL13	P26373	6	23.26	22.87	21.41	22.23	21.60	21.86	22.50	21.37	23.63	23.73
RPL13A	P40429	3	21.57	22.21	NAN	NAN	20.91	21.14	21.45	21.17	22.17	22.39
RPL14	P50914	5	NAN	NAN	NAN	NAN	22.31	22.60	22.79	22.03	23.47	23.66
RPL15	P61313	4	21.55	22.08	NAN	21.39	21.26	21.58	21.76	21.18	22.22	21.86
RPL17	P18621	6	23.41	23.87	21.89	22.24	21.88	21.64	22.75	21.98	23.44	23.77
RPL18	Q07020	5	22.65	NAN	NAN	NAN	22.06	22.30	22.57	21.59	23.71	23.27
RPL18A	Q02543	7	22.89	22.89	21.70	22.27	22.05	22.31	22.51	21.58	22.92	23.04
RPL22	P35268	3	21.91	22.26	21.36	21.59	21.28	NAN	21.42	22.41	21.55	21.76
RPL23A	P62750	5	22.07	22.57	22.23	22.18	20.80	20.75	21.87	21.11	22.59	22.57
RPL24	P83731	5	21.77	22.06	NAN	NAN	20.82	20.93	21.46	21.12	22.03	22.49
RPL26L1	Q9UNX3	3	21.19	21.38	20.54	NAN	20.67	20.06	21.07	20.67	21.41	21.41
RPL28	P46779	4	NAN	NAN	NAN	NAN	NAN	NAN	21.65	20.31	NAN	21.89
RPL3	P39023	12	23.99	24.58	23.18	22.82	22.09	22.13	23.21	21.98	23.86	24.04
RPL30	P62888	2	NAN	23.12	NAN	NAN	21.56	NAN	21.65	19.99	22.05	NAN
RPL31	P62899	3	22.59	22.50	NAN	21.32	21.05	20.83	NAN	NAN	22.25	22.30
RPL34	P49207	4	22.35	21.78	NAN	21.05	21.08	NAN	21.73	19.94	21.95	21.15
RPL35A	P18077	2	NAN	NAN	NAN	NAN	20.07	20.24	19.84	20.18	NAN	20.60
RPL36	Q9Y3U8	3	NAN	NAN	NAN	NAN	20.51	20.41	20.99	20.13	22.04	22.35
RPL4	P36578	12	23.97	24.68	21.57	22.67	22.23	21.83	23.12	21.65	23.85	24.33
RPL5	P46777	6	21.21	21.53	NAN	NAN	21.31	20.77	21.07	21.40	21.83	22.01
RPL6	Q02878	9	22.37	23.41	21.34	23.40	21.66	21.79	22.72	22.05	23.79	23.93
RPL7	P18124	5	NAN	22.83	NAN	21.51	21.01	NAN	22.12	21.20	22.71	22.78
RPL7A	P62424	8	23.36	23.94	NAN	22.50	21.66	21.63	22.74	21.82	23.18	24.15
RPL8	P62917	4	22.96	23.59	22.21	22.56	21.77	21.47	21.50	21.38	22.69	22.34
RPL9	P32969	6	NAN	NAN	NAN	NAN	21.13	21.10	21.93	22.10	21.49	21.40
RPLP0	P05388	7	NAN	20.73	NAN	NAN	20.41	20.24	20.08	21.40	20.40	20.96
RPLP2	P05387	3	NAN	NAN	NAN	NAN	NAN	NAN	19.73	21.34	NAN	19.66
RPN1	P04843	18	NAN	NAN	NAN	21.49	20.35	21.00	23.72	23.21	23.61	24.03
RPP30	P78346	3	NAN	NAN	NAN	NAN	19.38	NAN	19.66	NAN	19.50	19.57
RPRD1B	Q9NQG5	6	NAN	NAN	NAN	NAN	20.13	19.67	20.22	19.84	NAN	20.14

RPS10	P46783	5	22.00	21.72	20.85	21.04	22.77	23.01	22.43	21.51	21.98	21.56
RPS11	P62280	8	22.60	22.79	NAN	NAN	20.88	21.26	22.14	22.04	22.47	22.47
RPS12	P25398	6	21.04	21.33	20.73	21.12	21.12	20.81	21.32	20.70	21.31	21.99
RPS13	P62277	4	21.09	23.90	22.59	22.47	21.78	22.03	21.63	21.28	21.99	22.02
RPS14	P62263	5	23.51	23.53	22.13	23.00	23.04	23.34	23.28	22.26	22.84	23.28
RPS16	P62249	5	NAN	22.07	NAN	21.83	22.01	22.01	21.34	22.13	22.37	22.24
RPS17	P08708	4	NAN	NAN	NAN	NAN	20.41	20.68	20.84	NAN	20.73	20.96
RPS18	P62269	6	21.85	21.62	21.22	22.08	21.96	22.04	22.05	21.64	21.96	22.32
rps2	P15880	8	NAN	NAN	NAN	NAN	21.47	21.64	22.51	21.83	22.89	22.79
RPS23	P62266	3	NAN	NAN	NAN	NAN	21.02	20.57	21.13	20.30	21.55	21.58
RPS24	P62847	3	NAN	NAN	NAN	NAN	19.69	20.28	20.09	NAN	NAN	21.25
RPS25	P62851	3	21.70	21.91	NAN	21.33	21.55	21.28	21.75	20.88	NAN	22.86
RPS26	P62854	2	NAN	NAN	NAN	NAN	20.94	20.50	21.05	20.49	21.48	21.82
RPS27A	P62979	6	26.37	25.95	27.31	27.74	28.40	28.54	27.99	28.46	28.71	28.75
RPS27L	Q71UM5	3	NAN	21.39	NAN	21.45	21.65	NAN	21.01	21.09	21.47	21.02
RPS3	P23396	10	23.24	23.38	22.08	22.80	22.11	22.23	22.61	23.70	23.26	23.62
RPS3A	P61247	8	23.09	23.06	20.91	21.84	21.67	21.79	22.29	21.93	22.91	23.35
RPS4X	P62701	14	22.74	23.01	21.73	22.34	22.48	22.55	23.01	22.64	23.96	23.76
RPS4Y1	P22090	10	NAN	NAN	NAN	NAN	19.33	19.61	19.37	NAN	NAN	19.84
RPS5	P46782	8	21.45	NAN	21.98	22.68	23.19	22.95	22.17	22.30	22.17	22.74
RPS6	P62753	6	22.32	22.27	NAN	20.97	20.30	20.78	20.99	20.52	21.64	22.28
RPS6KA4	O75676	19	NAN	NAN	20.48	21.70	23.08	23.41	22.90	22.62	21.17	21.73
RPS7	P62081	5	NAN	NAN	NAN	NAN	22.66	22.20	22.26	22.18	22.55	22.83
RPS8	P62241	7	22.99	23.36	21.63	22.59	22.36	21.81	22.86	22.21	23.60	23.61
RPS9	P46781	7	21.89	22.56	21.99	22.57	21.79	21.62	22.19	22.14	22.42	23.06
RPSA	P08865	9	NAN	23.08	22.55	22.81	22.40	22.40	22.43	23.61	22.67	22.96
RRAGA	Q7L523	2	NAN	NAN	NAN	NAN	NAN	NAN	18.81	18.80	NAN	18.66
RRBP1	Q9P2E9	5	NAN	NAN	NAN	19.94	NAN	NAN	18.72	NAN	19.62	19.21
RRP1	P05386	7	NAN	20.10	NAN	20.49	20.66	21.15	20.67	20.61	21.01	20.73
RRP36	Q96EU6	3	NAN	NAN	NAN	NAN	18.86	18.58	NAN	NAN	NAN	NAN
RRP9	O43818	16	NAN	NAN	23.71	24.16	24.04	24.04	24.02	23.74	23.76	23.78
RSL1D1	O76021	5	NAN	NAN	NAN	NAN	20.70	19.98	20.42	NAN	21.50	20.91
RTCB	Q9Y3I0	17	21.64	22.75	22.94	23.53	23.31	23.16	23.48	23.00	23.31	23.75
RTF1	Q92541	13	NAN	NAN	NAN	21.38	22.21	22.25	21.70	22.04	NAN	21.74
RTFDC1	Q9BY42	7	NAN	NAN	NAN	NAN	20.71	20.77	20.71	20.71	NAN	NAN
RTRAF	Q9Y224	10	NAN	21.63	22.13	21.59	21.54	21.63	21.88	21.84	21.91	21.83
RUNX1	Q01196	12	NAN	NAN	22.86	23.19	24.52	24.86	23.29	23.67	21.53	22.96
RUNX3	Q13761	3	NAN	NAN	NAN	NAN	NAN	NAN	19.70	19.61	NAN	NAN
RUVBL1	Q9Y265	14	NAN	NAN	NAN	22.06	21.60	21.28	21.83	22.03	22.08	22.06
RUVBL2	Q9Y230	10	NAN	NAN	NAN	21.83	22.31	22.20	22.83	22.44	22.79	22.30
RXRA	P19793	14	NAN	NAN	21.29	21.23	23.26	23.14	22.63	22.23	20.41	20.80
S100A13	Q99584	2	NAN	NAN	NAN	NAN	NAN	NAN	19.22	18.80	NAN	19.81
S100A16	Q96FQ6	6	NAN	NAN	20.23	NAN	20.99	NAN	20.78	24.85	20.34	NAN
S100A4	P26447	2	NAN	NAN	NAN	NAN	20.32	20.84	21.18	20.90	21.20	NAN
S100A6	P06703	2	NAN	NAN	NAN	NAN	21.61	21.46	22.25	22.25	NAN	NAN
SAE1	Q9UBE0	9	NAN	NAN	NAN	NAN	20.87	20.79	20.59	NAN	NAN	NAN
SALL2	Q9Y467	12	24.76	24.01	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
SALL4	Q9UJQ4	18	25.38	24.89	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
SAMHD1	Q9Y3Z3	6	NAN	NAN	NAN	NAN	18.94	NAN	20.07	19.65	NAN	19.99
SAR1A	Q9NR31	4	NAN	NAN	21.82	21.87	21.10	21.32	21.72	21.36	22.13	22.45
SARNP	P82979	5	NAN	22.06	NAN	21.75	20.70	21.22	21.20	21.28	NAN	21.93
SART1	O43290	9	NAN	NAN	NAN	NAN	19.97	19.84	20.36	19.77	NAN	20.17
SATB2	Q9UPW6	24	NAN	NAN	22.82	24.04	24.15	24.30	24.07	23.65	23.42	23.38
SBDS	Q9Y3A5	9	NAN	NAN	NAN	NAN	21.00	20.92	21.61	20.99	21.70	21.75
SBNO1	A3KN83	10	NAN	NAN	NAN	NAN	NAN	NAN	19.52	19.22	NAN	NAN
SBNO2	Q9Y2G9	23	NAN	NAN	NAN	21.40	24.81	24.80	22.03	22.20	20.19	20.25
SBSN	Q6UWP8	23	19.89	20.30	26.38	23.01	19.13	18.53	20.62	21.37	20.99	19.91
SCAF11	Q99590	4	18.44	NAN	NAN	NAN	19.06	NAN	18.94	18.63	NAN	18.43
SCAI	Q8N9R8	13	NAN	NAN	NAN	NAN	21.96	22.61	20.37	20.76	NAN	NAN
SCML2	Q9UQR0	4	NAN	NAN	NAN	NAN	18.42	18.73	19.11	NAN	NAN	NAN
SCNM1	Q9BWG6	5	NAN	NAN	NAN	NAN	21.12	22.32	NAN	20.15	NAN	NAN
SDAD1	Q9NVU7	6	NAN	NAN	NAN	NAN	19.87	19.85	19.01	NAN	NAN	NAN
SDE2	Q6IQ49	4	NAN	NAN	NAN	NAN	19.88	19.69	19.37	NAN	NAN	NAN
SEC13	P55735	2	NAN	NAN	NAN	NAN	20.29	NAN	19.77	20.52	NAN	NAN
SEC22B	O75396	6	NAN	NAN	NAN	NAN	NAN	21.02	21.85	21.21	22.69	22.23
SEC23A	Q15436	7	NAN	NAN	21.16	21.67	20.31	20.85	21.41	20.99	21.41	22.00
SEH1L	Q96EE3	4	NAN	NAN	NAN	NAN	20.07	20.15	20.20	19.72	NAN	NAN
SELENOH	Q8IZQ5	4	NAN	NAN	NAN	NAN	21.51	21.00	20.54	20.28	NAN	NAN
SEPHS1	P49903	6	NAN	NAN	NAN	NAN	20.16	19.97	NAN	20.18	NAN	NAN
SEPT7	Q16181	6	NAN	NAN	NAN	NAN	NAN	21.16	21.16	NAN	22.34	22.18

SERBP1	Q8NC51	7	22.85	22.89	NAN	NAN	20.02	18.91	20.18	NAN	20.05	21.57
SERPINB2	P05120	5	NAN	NAN	20.53	19.84	19.69	19.61	19.87	21.11	NAN	19.98
SERPINH1	P50454	11	NAN	NAN	NAN	21.18	19.89	19.98	21.15	21.16	21.93	22.85
SESN2	P58004	6	NAN	NAN	NAN	NAN	19.29	19.54	19.40	NAN	NAN	NAN
SET	Q01105	8	25.87	25.03	23.69	24.78	24.41	24.61	25.13	24.79	24.73	24.66
SF1	Q15637	20	21.33	23.42	25.12	25.35	26.33	26.35	26.19	26.38	24.43	24.64
SF3A2	Q15428	2	NAN	NAN	NAN	NAN	NAN	NAN	18.38	18.27	NAN	NAN
SF3B1	O75533	13	NAN	NAN	NAN	NAN	NAN	20.16	20.98	20.78	20.71	20.87
SF3B2	Q13435	14	NAN	NAN	NAN	21.08	20.57	21.25	20.97	20.70	NAN	20.32
SF3B3	Q15393	13	20.67	21.57	NAN	21.05	21.63	21.70	22.38	21.84	21.23	21.56
SF3B4	Q15427	4	NAN	NAN	21.93	NAN	20.79	21.61	21.84	21.25	20.55	20.54
SF3B6	Q9Y3B4	4	NAN	NAN	NAN	NAN	20.96	20.86	20.80	21.01	NAN	20.65
SFPQ	P23246	33	26.97	28.43	29.43	29.81	30.01	30.30	29.01	29.75	28.69	28.78
SFRS4	Q08170	4	22.56	21.29	NAN	21.39	NAN	NAN	21.14	NAN	NAN	NAN
SH3BGRL3	Q9H299	3	NAN	NAN	21.57	NAN	22.07	21.69	21.97	22.10	21.83	21.61
SIN3A	Q96ST3	8	NAN	NAN	NAN	NAN	18.91	19.14	19.98	19.07	NAN	NAN
SIN3B	O75182	5	NAN	NAN	NAN	NAN	19.06	18.82	NAN	NAN	NAN	18.86
SIRT6	Q8N6T7	9	NAN	NAN	NAN	21.76	21.55	20.93	21.31	20.92	NAN	20.36
SKI	P12755	30	NAN	NAN	23.90	24.45	25.96	26.27	24.67	24.71	23.52	23.99
SKIL	P12757	19	NAN	NAN	NAN	22.02	23.32	24.01	21.90	22.35	19.84	21.28
SKP1	P63208	7	NAN	22.20	NAN	NAN	21.07	21.24	21.28	20.93	21.08	21.45
SLBP	Q14493	3	NAN	NAN	NAN	NAN	21.00	21.15	20.59	21.00	19.71	20.09
SLFN5	Q08AF3	18	NAN	NAN	NAN	NAN	23.09	23.37	23.08	22.81	23.52	23.32
SLU7	O95391	14	NAN	NAN	NAN	21.06	22.68	22.68	21.41	21.50	NAN	21.09
SMAD1	Q15797	5	NAN	NAN	NAN	NAN	19.75	19.77	NAN	19.14	NAN	NAN
SMAD2	Q15796	6	NAN	NAN	NAN	NAN	21.55	21.41	21.37	20.91	NAN	NAN
SMAD4	Q13485	15	22.96	NAN	23.53	23.70	25.22	25.35	23.56	23.78	22.25	22.89
SMARCA2	P51531	17	NAN	NAN	NAN	NAN	20.67	20.50	20.52	21.30	NAN	NAN
SMARCA4	P51532	36	25.17	24.36	23.58	24.36	24.79	24.86	24.56	24.03	22.78	23.36
SMARCA5	O60264	34	25.15	24.11	22.51	23.92	23.92	23.78	24.42	23.60	23.69	23.29
SMARCAD1	Q9H4L7	9	NAN	NAN	NAN	NAN	21.04	20.85	21.48	NAN	NAN	20.51
SMARCAL1	Q9NZC9	7	NAN	NAN	NAN	NAN	19.00	20.50	NAN	NAN	NAN	18.40
SMARCB1	Q12824	10	22.68	22.81	21.31	22.61	23.35	22.82	22.33	22.21	21.50	NAN
SMARCC1	Q92922	41	25.54	23.92	22.32	24.48	25.18	25.35	25.29	24.46	23.33	23.55
SMARCC2	Q8TAQ2	39	21.18	20.66	21.34	22.19	23.16	23.85	23.03	22.42	19.95	21.13
SMARCD1	Q96GM5	12	22.69	22.20	NAN	20.90	22.10	21.55	20.96	20.37	NAN	NAN
SMARCD2	Q92925	20	22.27	21.75	21.88	23.51	24.86	25.21	24.08	23.65	19.75	22.24
SMARCD3	Q6STE5	9	NAN	NAN	NAN	NAN	20.23	20.57	20.41	20.16	NAN	NAN
SMARCE1	Q969G3	13	23.30	23.82	23.93	22.90	23.74	23.45	23.74	22.69	21.40	21.67
SMC1A	Q14683	41	23.23	21.71	20.40	23.71	24.86	24.83	24.20	23.17	22.12	22.91
SMC3	Q9UQE7	39	23.56	22.79	21.47	23.83	24.73	24.89	24.63	23.79	21.36	22.80
SMC5	Q8IY18	9	NAN	NAN	NAN	NAN	20.66	21.19	20.25	NAN	NAN	19.61
SMC6	Q96SB8	8	NAN	NAN	NAN	NAN	20.76	20.19	19.73	NAN	NAN	NAN
SMCHD1	A6NHR9	38	23.33	22.93	23.42	24.55	23.43	23.39	23.99	23.42	24.03	23.94
SMNDC1	O75940	4	NAN	NAN	NAN	NAN	20.30	20.56	19.74	19.77	NAN	19.85
SMS	P52788	3	NAN	NAN	NAN	NAN	19.14	19.63	NAN	19.06	NAN	19.08
SMTN	P53814	16	NAN	NAN	20.94	22.10	20.98	21.29	21.97	22.20	22.25	22.36
SMU1	Q2TAY7	16	21.84	22.42	NAN	22.83	22.80	22.78	22.73	22.37	22.84	22.68
SMURF2	Q9HAU4	8	NAN	NAN	NAN	NAN	20.68	20.69	19.97	19.73	NAN	19.73
SNAI1	O95863	5	NAN	NAN	NAN	NAN	20.15	20.07	20.04	20.30	NAN	19.91
SND1	Q7KZF4	17	NAN	21.54	NAN	21.16	NAN	20.40	21.24	21.21	22.15	22.61
SNIP1	Q8TAD8	5	NAN	NAN	NAN	NAN	21.25	21.32	20.56	20.47	NAN	NAN
SNRNP200	O75643	38	21.23	22.94	21.82	21.85	21.97	22.14	23.33	22.19	22.06	22.84
SNRNP40	Q96DI7	8	NAN	NAN	NAN	NAN	21.48	21.54	21.37	21.72	21.07	21.30
SNRNP70	P08621	9	23.04	22.32	NAN	NAN	21.59	20.92	22.60	21.09	22.25	21.86
SNRPA	P09012	7	NAN	NAN	NAN	NAN	19.77	20.53	19.68	NAN	NAN	NAN
SNRPA1	P09661	6	NAN	NAN	20.20	20.54	NAN	21.27	NAN	NAN	NAN	NAN
SNRPC	P09234	3	NAN	21.60	21.87	22.41	22.62	23.03	22.16	22.40	21.11	21.17
SNRPD1	P62314	3	NAN	21.94	20.61	20.89	20.78	20.94	NAN	21.10	21.60	21.16
SNRPD2	P62316	7	21.50	22.42	NAN	NAN	20.53	20.46	21.50	20.68	NAN	21.46
SNRPD3	P62318	3	21.54	23.15	21.46	NAN	21.13	21.90	21.71	22.04	20.91	21.29
SNRPN	P63162	5	NAN	NAN	NAN	NAN	21.02	20.84	21.20	20.87	21.68	21.45
SNW1	Q13573	16	20.41	20.90	23.66	24.80	24.97	26.06	24.36	25.07	22.98	24.10
SNX3	O60493	4	NAN	NAN	NAN	NAN	NAN	21.13	21.12	20.70	NAN	NAN
SOX13	Q9UN79	7	NAN	NAN	NAN	NAN	20.38	20.53	NAN	NAN	NAN	NAN
SOX2	P48431	19	24.99	24.15	30.93	31.52	31.23	31.69	30.63	30.88	30.17	30.44
SP100	P23497	4	NAN	NAN	NAN	NAN	19.86	19.51	NAN	NAN	NAN	NAN
SPDL1	Q96EA4	4	NAN	NAN	NAN	NAN	18.71	19.03	19.54	NAN	NAN	NAN
SPIN	Q9Y657	4	NAN	20.57	NAN	NAN	20.30	20.59	20.20	20.04	19.75	19.82
SPOP	O43791	7	NAN	NAN	NAN	NAN	22.64	22.47	22.04	20.33	NAN	23.81

SPRR2D	P22532	6	22.42	NAN	NAN	21.41	20.16	NAN	19.59	26.80	21.17	21.34
SPTY2D1	Q68D10	18	NAN	NAN	NAN	NAN	22.65	23.01	21.72	21.65	20.11	20.82
SRBD1	Q8N5C6	19	NAN	NAN	NAN	NAN	23.13	23.21	22.00	21.11	20.79	21.62
SRI	P30626	10	NAN	NAN	NAN	NAN	23.99	24.30	23.12	23.31	22.09	23.09
SRM	P19623	8	NAN	NAN	20.92	21.21	21.34	21.12	21.05	21.02	21.41	NAN
SRP14	P37108	4	NAN	NAN	NAN	NAN	NAN	21.38	20.99	NAN	20.97	21.20
SRP9	P49458	2	NAN	NAN	NAN	NAN	20.09	20.10	NAN	20.01	NAN	NAN
SRRT	Q9BXP5	15	22.35	21.45	NAN	22.07	22.17	22.11	22.47	22.26	22.27	21.83
SRSF1	Q07955	11	24.32	24.72	21.65	23.99	22.01	20.94	23.32	21.45	23.99	22.81
SRSF10	O75494	5	22.02	NAN	NAN	NAN	20.86	21.07	21.72	NAN	21.81	21.63
SRSF2	Q01130	3	NAN	21.96	NAN	21.37	20.17	20.41	21.65	20.70	21.74	21.23
SRSF3	P84103	6	21.98	21.98	NAN	NAN	21.31	21.11	22.75	21.39	22.75	22.62
SRSF7	Q16629	7	25.13	24.84	21.62	23.42	22.78	21.81	23.79	21.78	23.69	23.53
SRSF9	Q13242	8	23.54	23.74	20.46	21.63	21.47	20.55	21.36	20.56	21.86	21.34
SS18	Q15532	6	21.78	NAN	NAN	NAN	21.82	22.80	21.44	21.78	NAN	20.41
SS18L1	O75177	3	NAN	NAN	NAN	NAN	19.46	19.45	NAN	NAN	NAN	NAN
SSB	P05455	10	NAN	21.95	NAN	21.18	21.00	20.76	21.78	21.35	22.03	22.21
SSBP3	Q9BWW4	3	NAN	NAN	NAN	NAN	20.93	21.10	20.84	20.79	NAN	NAN
SSBP4	Q9BWG4	3	NAN	NAN	NAN	NAN	22.74	22.66	22.01	21.44	NAN	NAN
SSR4	P51571	5	NAN	NAN	19.66	NAN	18.61	NAN	19.63	21.58	19.83	20.50
SSRP1	Q08945	21	25.28	24.34	24.35	25.28	27.16	27.18	26.07	25.67	24.81	25.06
SSU72	Q9NP77	6	NAN	NAN	NAN	21.40	21.36	21.39	21.00	20.86	20.62	20.78
STAG1	Q8WVM7	9	NAN	NAN	NAN	19.75	20.55	21.14	20.19	20.20	NAN	NAN
STAG2	Q8N3U4	7	NAN	NAN	NAN	NAN	19.69	19.87	19.63	NAN	NAN	NAN
STAT1	P42224	28	NAN	NAN	24.55	24.76	23.91	24.12	25.47	24.86	25.73	25.65
STAT3	P40763	35	20.09	21.85	25.30	26.50	27.19	27.93	26.30	27.75	25.34	26.47
STAT5A	P42229	18	NAN	NAN	19.87	20.91	22.94	23.68	22.72	22.97	NAN	20.13
STAT5B	P51692	15	NAN	NAN	20.42	NAN	NAN	20.17	19.50	19.75	NAN	NAN
STAT6	P42226	7	NAN	NAN	NAN	NAN	20.62	20.07	20.81	20.48	20.59	20.92
STIP1	P31948	9	NAN	NAN	NAN	19.90	21.77	21.98	20.72	20.42	NAN	NAN
STRAP	Q9Y3F4	10	NAN	NAN	NAN	21.39	20.09	20.37	21.53	21.70	20.24	20.99
STUB1	Q9UNE7	7	NAN	NAN	NAN	20.27	21.29	20.66	19.88	19.70	NAN	19.71
SUGP2	Q8IX01	12	NAN	20.55	NAN	20.69	21.38	21.57	21.33	20.68	NAN	NAN
SUGT1	Q9Y2Z0	5	NAN	NAN	NAN	NAN	19.84	19.83	19.15	NAN	NAN	19.56
SUI1	P41567	4	NAN	NAN	NAN	NAN	21.52	21.59	21.77	21.28	21.30	21.15
SUMO1	P63165	8	24.29	23.79	22.54	23.01	23.90	24.12	22.94	23.21	22.28	22.63
SUMO2	P61956	2	24.98	23.93	22.30	24.72	21.91	25.99	24.47	24.50	23.13	23.10
SUMO3	P55854	2	25.63	24.75	24.80	25.75	26.91	27.08	25.91	25.69	24.15	24.62
SUPT16H	Q9Y5B9	49	25.96	25.38	25.33	26.30	27.64	27.78	26.70	26.30	25.46	25.76
SUPT20H	Q8NEM7	2	NAN	NAN	NAN	NAN	18.68	18.82	NAN	NAN	NAN	NAN
SUPT5H	O00267	40	21.00	20.70	23.52	24.98	25.83	26.24	25.65	25.52	24.74	24.30
SUPT6H	Q7KZ85	43	20.28	20.38	19.80	22.62	23.39	24.35	24.52	23.90	24.07	23.11
SYF2	O95926	4	NAN	NAN	NAN	NAN	21.79	21.72	NAN	NAN	NAN	NAN
SYNCRIP	O60506	21	24.60	24.87	22.71	23.74	23.07	22.97	24.59	23.05	23.88	24.31
TAF15	Q92804	13	25.23	25.21	25.24	25.87	26.48	26.84	26.03	25.87	24.88	24.67
TAGLN	Q01995	17	NAN	NAN	25.20	25.76	25.30	25.36	26.04	25.94	26.41	25.90
TAGLN2	P37802	10	NAN	NAN	22.33	22.96	23.23	23.38	22.88	22.92	23.08	23.01
TALDO1	P37837	9	NAN	20.96	21.74	21.80	21.61	21.33	21.39	22.82	22.32	22.20
TAOK2	Q9UL54	15	NAN	NAN	21.37	NAN	21.66	21.48	21.43	21.47	NAN	NAN
TBCB	Q99426	4	19.37	NAN	NAN	19.10	NAN	NAN	19.53	19.49	19.46	NAN
TBL1X	O60907	11	NAN	NAN	NAN	NAN	19.61	20.06	19.24	19.28	NAN	NAN
TBL1XR1	Q9BZK7	16	21.78	20.61	22.52	23.55	24.54	24.54	24.29	23.35	22.13	23.09
TBL3	Q12788	11	NAN	NAN	NAN	NAN	22.18	21.66	21.06	20.91	NAN	21.00
TBX1	O43435	6	NAN	NAN	NAN	NAN	19.89	20.32	NAN	19.38	NAN	NAN
TBX15	Q96SF7	15	NAN	NAN	NAN	NAN	22.50	22.64	21.20	21.29	NAN	21.60
TBX18	O95935	6	NAN	NAN	NAN	NAN	20.28	20.18	NAN	NAN	NAN	NAN
TBX3	O15119	18	NAN	NAN	21.43	23.20	23.94	24.06	23.11	23.41	21.91	22.25
TBX5	Q99593	3	NAN	NAN	NAN	NAN	20.61	20.41	NAN	19.79	NAN	NAN
TCEA1	P23193	8	21.62	20.91	NAN	21.18	21.29	21.24	20.86	20.73	20.90	20.87
TCEAL4	Q96EI5	3	NAN	NAN	NAN	NAN	18.49	18.57	17.76	NAN	NAN	NAN
TCERG1	O14776	9	NAN	21.01	NAN	21.89	21.22	20.87	21.37	20.95	21.46	21.53
TCF12	Q99081	18	21.42	19.57	NAN	21.74	23.68	23.47	22.56	22.07	20.07	20.68
TCF19	Q9Y242	3	NAN	NAN	NAN	NAN	19.34	20.27	NAN	20.62	NAN	NAN
TCF20	Q9UGU0	60	19.73	21.51	22.34	23.13	26.41	26.58	25.12	24.72	19.68	22.44
TCF3	P15923	19	NAN	NAN	NAN	21.24	24.19	23.80	22.75	22.44	19.38	20.83
TCF4	P15884	9	21.31	20.71	NAN	NAN	21.49	21.77	20.74	20.75	NAN	19.98
TCP1	P17987	7	NAN	NAN	NAN	NAN	NAN	18.60	19.55	21.91	19.89	19.92
TDP43	Q13148	14	23.69	24.65	23.57	23.39	24.00	24.09	23.99	23.55	23.97	23.75
TEAD1	P28347	16	NAN	NAN	21.82	NAN	24.50	24.35	23.36	22.99	21.72	21.89
TEAD3	Q9NQB0	18	22.83	21.98	23.43	24.35	25.60	25.25	24.33	24.66	23.20	23.85

TEAD4	Q15561	11	NAN	NAN	NAN	NAN	22.36	22.74	21.85	20.86	NAN	19.92
TELO2	Q9Y4R8	18	NAN	NAN	NAN	21.21	23.03	23.00	22.74	22.42	21.13	20.44
TENT2	Q6PIY7	7	NAN	NAN	NAN	NAN	21.98	21.73	20.69	NAN	NAN	NAN
TES	Q9UGI8	10	NAN	NAN	NAN	21.23	20.50	20.69	21.02	20.75	NAN	21.56
TET2	Q6N021	6	NAN	NAN	NAN	NAN	19.39	19.41	NAN	NAN	NAN	NAN
TEX10	Q9NXF1	5	NAN	NAN	NAN	NAN	20.44	19.55	NAN	NAN	NAN	NAN
TFAP2C	Q92754	5	NAN	NAN	NAN	NAN	20.79	20.88	20.70	NAN	NAN	NAN
TFAP4	Q01664	8	NAN	NAN	21.17	22.20	23.72	23.65	22.60	21.99	19.89	19.77
TFCP2	Q12800	6	NAN	NAN	NAN	NAN	19.80	19.83	NAN	NAN	NAN	NAN
TFE3	P19532	5	NAN	NAN	NAN	NAN	19.96	19.78	NAN	19.29	NAN	NAN
TFEB	P19484	5	NAN	NAN	NAN	NAN	20.17	20.96	19.36	19.86	NAN	NAN
TFIP11	Q9UBB9	18	NAN	NAN	NAN	NAN	22.42	22.99	21.91	21.86	20.46	21.42
TGFB1I1	O43294	7	NAN	NAN	21.42	NAN	20.65	20.43	21.17	21.14	20.93	21.50
TGM2	P21980	10	NAN	NAN	NAN	20.82	NAN	19.43	20.82	19.76	22.20	20.66
THAP11	Q96EK4	4	NAN	NAN	NAN	NAN	21.02	20.60	NAN	NAN	NAN	NAN
THOC5	Q13769	3	NAN	NAN	NAN	NAN	19.52	19.59	NAN	NAN	NAN	NAN
THOC6	Q86W42	8	NAN	NAN	NAN	NAN	21.41	21.34	20.04	20.75	NAN	NAN
THRAP3	Q9Y2W1	12	20.93	20.94	NAN	NAN	19.65	NAN	20.87	NAN	20.46	21.13
THYN1	Q9P016	6	NAN	NAN	NAN	19.99	20.44	20.95	20.14	20.08	19.88	20.51
TIA1	P31483	7	NAN	NAN	NAN	NAN	20.68	20.78	20.44	20.12	NAN	NAN
TIAL1	Q01085	8	21.78	21.96	22.54	22.35	22.82	23.21	22.64	22.50	21.88	21.80
TIPRL	O75663	7	NAN	NAN	NAN	NAN	20.68	20.76	20.46	20.32	20.34	20.65
TKT	P29401	19	25.27	25.13	24.95	24.28	24.20	24.59	24.67	24.76	24.66	24.81
TLE1	Q04724	21	NAN	21.45	NAN	NAN	22.91	23.48	21.43	21.14	NAN	20.56
TLE3	Q04726	27	22.27	20.59	23.54	25.25	26.43	26.64	25.69	25.38	23.35	23.94
TLE4	Q04727	25	NAN	21.35	22.47	23.78	25.11	24.99	24.37	24.03	21.91	22.40
TLN1	Q9Y490	9	NAN	NAN	NAN	NAN	NAN	NAN	19.72	21.05	21.56	21.13
TMEM113	Q6UXN9	7	NAN	NAN	NAN	21.09	20.47	20.77	20.02	20.12	NAN	20.24
TMEM201	Q5SNT2	7	NAN	NAN	NAN	20.62	19.61	20.77	21.45	20.51	21.92	22.39
TMEM43	Q9BTV4	7	NAN	NAN	NAN	NAN	NAN	NAN	21.68	21.60	22.63	22.53
TMPO	P42167	27	23.91	23.58	23.74	25.32	24.10	24.27	25.80	24.66	25.60	25.78
TNIP2	Q8NFZ5	13	NAN	NAN	22.78	21.91	22.81	23.05	22.00	22.30	NAN	NAN
TNPO1	Q92973	35	21.04	21.26	24.99	25.47	26.32	26.60	25.97	26.25	24.30	24.87
TNPO2	O14787	27	NAN	NAN	20.33	22.30	23.86	24.08	23.75	23.86	22.52	21.98
TNPO3	Q9Y5L0	18	NAN	NAN	21.88	21.02	23.52	22.75	22.48	22.21	20.24	20.39
TNRC18	O15417	36	22.00	NAN	22.73	24.35	24.63	24.92	23.92	24.45	21.41	22.63
TOP1	P11387	27	24.33	23.62	24.18	25.09	24.93	25.09	24.77	24.02	24.36	24.63
TOP2A	P11388	38	24.90	24.44	22.03	23.16	21.82	21.92	23.83	22.94	22.75	22.87
TOP2B	Q02880	43	25.29	25.17	24.12	24.72	25.01	24.95	24.98	24.32	24.18	24.77
TOP3A	Q13472	10	NAN	NAN	NAN	NAN	20.74	21.38	20.38	20.16	NAN	19.75
TPI1	P60174	15	24.07	23.61	24.00	21.72	22.86	22.73	22.14	25.65	23.39	23.12
TPM3	P06753	11	NAN	NAN	21.51	21.97	20.49	22.29	22.02	23.31	22.72	22.34
TPM4	P67936	9	NAN	NAN	NAN	20.56	19.66	19.32	21.16	20.46	20.51	21.34
TPR	P12270	9	NAN	NAN	20.74	19.66	NAN	NAN	19.28	19.15	19.59	19.91
TRA2A	Q13595	5	NAN	NAN	NAN	NAN	19.00	18.75	21.14	NAN	21.75	20.33
TRA2B	P62995	6	22.13	22.65	NAN	21.16	20.57	19.88	22.92	20.50	21.95	22.16
TRAF3IP2	O43734	20	NAN	NAN	NAN	NAN	24.31	24.61	22.33	21.90	NAN	19.50
TRAF4	Q9BUZ4	5	NAN	NAN	NAN	NAN	19.12	19.80	19.76	NAN	NAN	NAN
TRAPPC2L	Q9UL33	2	NAN	NAN	NAN	NAN	19.73	20.12	NAN	NAN	NAN	NAN
TRAPPC4	Q9Y296	4	NAN	NAN	NAN	NAN	21.25	20.65	NAN	19.90	NAN	NAN
TRERF1	Q96PN7	11	NAN	NAN	NAN	NAN	22.45	22.88	21.31	21.10	NAN	NAN
TRIM11	Q96F44	11	NAN	NAN	NAN	NAN	22.70	22.98	22.17	22.17	NAN	22.40
TRIM22	Q8IYM9	19	NAN	NAN	24.43	24.95	26.56	26.92	25.39	25.24	24.16	24.48
TRIM24	O15164	25	23.70	23.42	NAN	21.98	23.14	23.82	22.51	22.47	NAN	20.83
TRIM25	Q14258	12	NAN	NAN	19.73	20.87	NAN	19.32	19.87	21.09	20.09	19.53
TRIM28	Q13263	34	26.65	27.40	24.78	27.01	27.03	26.93	27.38	26.57	27.02	27.09
TRIM32	Q13049	10	NAN	NAN	NAN	NAN	21.71	21.76	NAN	NAN	NAN	NAN
TRIM33	Q9UPN9	32	23.66	23.63	23.84	24.41	26.10	25.95	24.62	24.27	22.93	23.06
TRIM35	Q9UPQ4	8	NAN	NAN	NAN	NAN	21.30	21.86	20.07	20.16	NAN	NAN
TRIM65	Q6PJ69	7	NAN	NAN	NAN	NAN	20.23	20.52	NAN	19.72	NAN	NAN
TRIM8	Q9BZR9	15	NAN	NAN	NAN	21.52	23.61	23.84	22.14	22.37	20.42	21.80
TRIP12	Q14669	20	NAN	NAN	21.75	22.50	21.22	20.89	22.36	21.21	22.29	22.65
TRIP6	Q15654	18	NAN	NAN	23.68	24.00	24.78	24.98	24.07	24.32	22.91	23.22
TRIR	Q9BQ61	4	NAN	NAN	NAN	NAN	21.73	21.88	21.18	21.38	21.37	20.93
TRMT1	O75648	9	NAN	NAN	NAN	NAN	20.47	20.27	20.39	20.09	20.55	20.57
TRPS1	Q9UHF7	15	NAN	NAN	NAN	21.35	21.49	21.50	21.86	20.86	19.49	20.68
TRRAP	Q9Y4A5	35	NAN	NAN	NAN	20.52	22.08	23.46	21.92	21.45	NAN	19.67
TSEN34	Q9BSV6	10	NAN	NAN	NAN	NAN	22.69	22.50	21.42	21.78	NAN	21.06
TSG101	Q99816	7	NAN	NAN	NAN	NAN	21.31	21.86	20.82	21.24	NAN	NAN
TSR1	Q2NL82	14	NAN	NAN	NAN	21.77	21.37	21.93	21.78	21.57	21.68	22.14

TTLL12	Q14166	10	NAN	NAN	NAN	21.04	21.30	21.70	21.91	21.58	20.58	20.22
TUBA1A	Q71U36	21	NAN	NAN	22.79	NAN	NAN	NAN	21.69	21.35	23.02	21.88
TUBA1B	P68363	21	25.44	26.34	26.27	26.67	25.34	25.31	26.42	26.50	27.39	26.96
TUBB	P07437	18	22.95	23.92	24.15	23.78	22.99	23.35	22.77	23.10	24.67	24.15
TUBB2C	P68371	19	24.57	25.25	25.85	25.98	24.85	25.08	25.69	26.02	26.77	26.38
TUBB6	Q9BUF5	15	NAN	NAN	22.43	23.08	21.08	21.41	22.36	22.38	23.36	22.72
TUFM	P49411	11	21.76	20.79	NAN	NAN	NAN	20.12	NAN	20.64	NAN	NAN
TWF2	Q6IBS0	5	NAN	NAN	NAN	NAN	20.54	20.69	21.18	20.60	NAN	NAN
TWIST2	Q8WVJ9	2	NAN	NAN	NAN	NAN	21.75	21.42	NAN	NAN	NAN	NAN
TXN	P10599	8	23.86	23.16	25.21	24.57	24.57	24.96	24.49	25.35	25.18	25.10
TXNDC5	Q8NBS9	4	NAN	NAN	NAN	NAN	NAN	NAN	19.49	19.19	NAN	20.00
TXNL1	O43396	6	NAN	NAN	NAN	NAN	21.14	20.60	20.45	21.31	NAN	20.70
TXNRD1	Q16881	5	NAN	NAN	NAN	NAN	20.34	19.64	20.27	20.36	20.41	20.65
U2AF1	Q01081	9	NAN	22.73	22.54	23.48	24.26	24.66	24.63	24.31	23.88	23.82
U2AF2	P26368	15	23.28	24.16	24.08	23.62	24.44	24.60	24.64	24.31	23.75	23.68
U2SURP	O15042	10	20.78	20.91	NAN	21.76	20.93	20.58	21.51	20.95	21.27	20.97
UBA1	P22314	17	NAN	20.42	21.50	22.09	21.67	21.42	22.03	22.70	22.83	22.69
UBE2I	P63279	8	21.80	22.06	22.06	22.68	23.93	23.53	22.30	22.37	21.03	21.94
UBE2L3	P68036	3	NAN	NAN	NAN	NAN	19.13	NAN	19.88	19.23	NAN	NAN
UBE2M	P61081	5	NAN	NAN	NAN	NAN	20.09	20.20	19.37	20.02	NAN	19.54
UBE2N	P61088	3	NAN	NAN	NAN	NAN	20.37	20.42	20.28	21.10	NAN	20.74
UBE2S	Q16763	3	NAN	NAN	NAN	NAN	20.91	21.18	21.07	20.85	20.49	20.59
UBE2V1	Q13404	3	NAN	NAN	20.22	NAN	20.35	NAN	20.92	20.68	20.34	NAN
UBTF	P17480	15	22.98	22.15	20.72	22.40	22.98	23.48	23.49	22.74	21.88	22.08
UBXN1	Q04323	2	NAN	NAN	NAN	NAN	NAN	19.34	19.50	19.63	19.46	19.05
UCHL1	P09936	3	22.17	NAN	NAN	20.74	20.81	20.69	21.11	20.68	NAN	20.50
UCHL3	P15374	4	NAN	NAN	NAN	NAN	NAN	NAN	18.27	19.76	NAN	NAN
UFD1L	Q92890	5	NAN	NAN	20.45	20.70	20.66	21.02	21.09	21.10	NAN	NAN
UGDH	O60701	8	NAN	NAN	NAN	NAN	19.93	19.78	20.16	20.46	21.76	21.25
UHMK1	Q8TAS1	16	NAN	NAN	20.41	22.61	24.82	24.97	22.64	22.71	21.61	21.80
UHRF1	Q96T88	26	NAN	21.14	NAN	22.26	21.99	22.54	23.04	22.32	22.02	22.56
UHRF2	Q96PU4	19	NAN	NAN	21.04	22.82	23.87	23.57	23.35	22.70	22.00	22.33
UIMC1	Q96RL1	3	NAN	NAN	NAN	NAN	18.72	18.13	NAN	NAN	NAN	NAN
UPF1	Q92900	6	NAN	NAN	20.09	20.13	NAN	NAN	NAN	20.09	NAN	NAN
USF1	P22415	6	NAN	NAN	NAN	NAN	20.97	20.79	20.77	21.11	NAN	NAN
USP11	P51784	10	19.22	NAN	NAN	NAN	19.42	19.70	20.22	20.16	NAN	NAN
USP15	Q9Y4E8	14	23.04	23.12	NAN	21.45	NAN	NAN	21.09	NAN	NAN	NAN
USP22	Q9UPT9	4	NAN	NAN	NAN	NAN	20.33	20.39	20.22	NAN	NAN	NAN
USP39	Q53GS9	5	NAN	NAN	21.86	NAN	20.79	20.55	20.88	20.27	NAN	20.42
USP48	Q86UV5	14	NAN	NAN	NAN	20.84	21.03	21.44	21.59	21.17	20.57	21.34
USP5	P45974	11	NAN	NAN	NAN	21.27	20.41	21.01	21.46	21.78	20.40	20.96
USP7	Q93009	14	20.27	21.69	21.83	NAN	20.92	20.95	21.94	20.80	21.18	20.93
UTP4	Q969X6	7	NAN	NAN	NAN	20.00	20.14	20.13	19.84	19.84	NAN	NAN
UTP6	Q9NYH9	6	NAN	NAN	NAN	NAN	20.56	20.85	20.27	NAN	NAN	NAN
UVSSA	Q2YD98	10	NAN	NAN	NAN	NAN	20.38	20.89	20.55	20.76	NAN	20.08
VCL	P18206	33	NAN	NAN	24.05	24.11	21.87	21.68	23.38	23.85	23.69	23.88
VCP	P55072	28	NAN	NAN	23.73	20.89	21.28	20.56	22.28	24.79	22.31	22.22
VDR	P11473	5	NAN	NAN	NAN	NAN	19.50	19.99	NAN	NAN	NAN	NAN
VENTX	O95231	5	NAN	NAN	NAN	NAN	21.20	20.91	20.78	NAN	NAN	NAN
VEZF1	Q14119	6	NAN	NAN	NAN	NAN	19.38	19.62	NAN	19.11	NAN	NAN
VGLL3	A8MV65	3	NAN	NAN	NAN	NAN	21.04	20.59	20.08	NAN	NAN	NAN
VGLL4	Q14135	4	NAN	NAN	NAN	NAN	19.33	20.15	NAN	NAN	NAN	NAN
VPS28	Q9UK41	5	NAN	NAN	NAN	NAN	20.35	20.67	20.41	20.67	NAN	20.16
VPS37A	Q8NEZ2	6	NAN	NAN	NAN	19.86	19.71	19.62	20.33	20.24	NAN	NAN
VPS37B	Q9H9H4	2	NAN	NAN	NAN	NAN	NAN	19.42	19.75	19.71	NAN	NAN
VPS4B	O75351	8	NAN	NAN	21.00	21.05	20.86	21.19	20.78	21.34	20.98	21.01
VRTN	Q9H8Y1	12	24.44	24.61	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
WBP4	O75554	3	NAN	NAN	NAN	NAN	NAN	19.02	19.33	19.19	NAN	NAN
WDR12	Q9GZL7	6	NAN	NAN	NAN	NAN	20.69	20.67	20.85	20.22	20.40	20.62
WDR13	Q9H1Z4	4	NAN	NAN	NAN	NAN	20.05	20.89	NAN	NAN	NAN	NAN
WDR25	Q64LD2	8	NAN	NAN	NAN	NAN	20.91	21.27	NAN	20.15	NAN	NAN
WDR3	Q9UNX4	12	NAN	NAN	NAN	19.84	20.87	21.49	20.31	19.73	NAN	19.14
WDR33	Q9C0J8	8	NAN	NAN	NAN	NAN	19.74	19.89	20.41	19.74	19.78	NAN
WDR36	Q8NI36	13	21.03	NAN	NAN	NAN	20.68	21.58	19.72	19.91	20.55	20.53
WDR5	P61964	14	22.09	22.32	22.90	23.95	25.20	25.06	24.28	24.21	22.98	22.95
WDR55	Q9H6Y2	12	NAN	NAN	NAN	22.35	22.93	23.02	22.67	21.41	21.54	21.46
WDR6	Q9NNW5	4	NAN	NAN	NAN	NAN	19.55	20.05	19.04	18.95	NAN	NAN
WDR61	Q9GZS3	5	NAN	NAN	NAN	NAN	NAN	20.54	20.75	21.10	NAN	NAN
WDR70	Q9NW82	6	NAN	NAN	NAN	NAN	21.39	20.99	21.21	20.57	NAN	NAN
WDR74	Q6RFH5	5	NAN	NAN	NAN	NAN	21.16	20.52	NAN	19.47	NAN	NAN

WIZ	O95785	26	23.06	21.91	22.58	23.26	23.00	23.15	22.65	22.33	21.93	21.98
WRNIP1	Q96S55	9	NAN	NAN	NAN	NAN	20.28	20.37	20.76	20.09	NAN	20.59
WWTR1	Q9GZV5	11	19.90	NAN	21.04	23.25	23.84	23.70	22.48	22.33	20.29	21.44
XIAP	P98170	4	NAN	NAN	NAN	NAN	20.02	19.68	19.63	19.14	NAN	NAN
XPC	Q01831	10	NAN	NAN	NAN	NAN	21.19	21.68	20.68	20.38	21.04	20.95
XPO1	O14980	38	22.50	23.22	24.19	24.73	25.13	25.17	25.13	24.83	23.84	24.12
XPO4	Q9C0E2	8	NAN	NAN	NAN	NAN	19.57	19.79	NAN	19.06	NAN	NAN
XPO5	Q9HAV4	19	20.15	NAN	21.37	21.31	21.80	21.86	22.21	21.25	20.95	21.16
XPO6	Q96QU8	17	NAN	NAN	20.68	21.26	22.64	23.51	22.42	22.27	NAN	NAN
XPO7	Q9UIA9	12	NAN	NAN	NAN	NAN	21.34	21.46	21.34	20.64	NAN	NAN
XPOT	O43592	22	19.97	NAN	20.88	21.45	23.61	23.24	22.96	22.77	20.20	21.97
XRCC5	P13010	29	24.15	25.14	23.13	24.36	23.60	23.91	25.27	24.54	24.63	24.84
XRCC6	P12956	27	25.52	25.63	24.66	24.98	24.97	25.24	25.70	25.19	25.48	25.88
XRN2	Q9H0D6	31	22.48	23.07	23.26	23.89	24.87	25.20	24.32	23.98	23.20	23.56
YAP1	P46937	15	22.56	20.52	23.83	24.44	25.30	25.58	24.00	24.70	23.37	23.36
YBX1	P67809	5	20.74	20.27	NAN	20.87	19.47	19.27	20.36	19.23	19.76	20.54
YLPM1	P49750	14	20.55	21.02	21.42	21.16	20.20	20.47	20.87	20.94	20.63	20.27
YWHAB	P31946	11	NAN	NAN	22.66	23.27	22.62	22.74	22.86	23.26	22.40	22.46
YWHAE	P62258	16	23.62	24.22	23.94	23.88	24.47	24.90	24.62	25.37	23.60	23.96
YWHAG	P61981	12	21.74	NAN	NAN	23.35	22.64	22.47	23.00	23.49	22.56	23.02
YWHAH	Q04917	8	NAN	NAN	NAN	NAN	20.39	20.95	21.02	20.87	NAN	20.81
YWHAQ	P27348	14	22.74	22.29	23.20	23.00	22.98	23.58	23.54	23.64	23.21	23.73
YWHAZ	P63104	13	22.31	22.39	23.23	22.77	23.83	23.94	23.87	25.34	23.37	24.08
YY1	P25490	10	21.99	NAN	NAN	21.75	21.58	21.55	21.70	21.42	21.44	21.67
ZBTB10	Q96DT7	13	NAN	NAN	NAN	NAN	22.01	22.75	21.54	20.96	NAN	20.28
ZBTB20	Q9HC78	16	NAN	NAN	21.50	NAN	23.27	23.99	21.40	21.23	19.95	20.30
ZBTB33	Q86T24	8	NAN	NAN	NAN	NAN	20.48	20.74	20.38	20.09	NAN	NAN
ZBTB4	Q9P1Z0	16	NAN	NAN	NAN	NAN	23.14	23.22	21.08	20.98	NAN	17.70
ZBTB40	Q9NUA8	7	NAN	NAN	NAN	NAN	19.90	20.08	20.28	19.77	NAN	NAN
ZBTB43	O43298	7	NAN	NAN	NAN	NAN	21.49	21.64	20.78	20.55	NAN	NAN
ZBTB44	Q8NCP5	4	NAN	NAN	NAN	NAN	19.43	19.88	19.55	18.94	NAN	NAN
ZBTB5	O15062	10	NAN	NAN	NAN	NAN	21.61	22.02	21.11	20.58	NAN	NAN
ZBTB7A	O95365	10	NAN	NAN	NAN	20.56	21.59	22.00	21.67	21.07	NAN	21.00
ZBTB9	Q96C00	7	NAN	NAN	NAN	20.99	22.59	22.63	21.41	20.65	NAN	20.76
ZC3H14	Q6PJT7	10	NAN	NAN	NAN	20.85	20.85	21.35	21.25	20.87	NAN	19.83
ZFHX1B	O60315	8	NAN	NAN	NAN	NAN	20.10	20.32	20.12	19.78	NAN	NAN
ZFHX3	Q15911	9	NAN	NAN	NAN	NAN	19.63	19.81	19.51	19.40	NAN	NAN
ZFR	Q96KR1	13	NAN	NAN	20.58	21.83	21.21	21.42	21.67	21.25	20.46	20.58
ZGPAT	Q8N5A5	12	NAN	NAN	NAN	20.91	20.50	20.92	20.69	20.29	20.04	20.03
ZIC2	O95409	2	22.31	21.37	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
ZKSCAN1	P17029	9	NAN	NAN	NAN	NAN	21.80	22.18	20.90	21.19	20.19	20.58
ZKSCAN8	Q15776	4	NAN	NAN	NAN	NAN	19.80	19.31	NAN	NAN	NAN	NAN
ZMIZ1	Q9ULJ6	25	NAN	NAN	23.38	24.98	26.97	26.97	25.81	25.96	23.62	23.87
ZMIZ2	Q8NF64	17	NAN	NAN	NAN	23.19	24.31	24.91	22.60	23.13	21.27	21.07
ZMYM4	Q5VZL5	26	22.43	21.22	20.58	22.13	22.68	23.02	22.98	22.17	21.92	22.76
ZNF106	Q9H2Y7	21	NAN	NAN	NAN	NAN	22.00	22.37	20.26	19.20	NAN	NAN
ZNF148	Q9UQR1	14	NAN	NAN	NAN	20.84	21.83	21.44	22.21	21.52	22.14	22.03
ZNF198	Q9UBW7	14	23.46	22.97	NAN	20.90	20.82	20.72	21.23	19.99	NAN	NAN
ZNF207	O43670	5	21.02	NAN	21.27	22.51	22.03	21.86	22.38	21.63	21.66	21.73
ZNF217	O75362	10	20.71	20.84	NAN	21.21	20.57	20.71	20.87	20.31	NAN	NAN
ZNF219	Q9P2Y4	7	19.89	19.49	NAN	NAN	19.56	19.73	NAN	19.35	NAN	NAN
ZNF239	Q16600	2	NAN	NAN	NAN	NAN	18.62	18.92	NAN	NAN	NAN	NAN
ZNF24	P17028	13	NAN	NAN	NAN	NAN	22.95	22.90	21.85	22.16	21.23	21.41
ZNF281	Q9Y2X9	26	21.53	21.91	20.25	20.12	23.58	24.41	21.97	22.37	20.04	20.96
ZNF282	Q9UDV7	6	NAN	NAN	NAN	NAN	21.37	21.08	20.15	NAN	NAN	NAN
ZNF292	O60281	12	NAN	NAN	NAN	NAN	19.91	19.92	19.53	19.51	NAN	NAN
ZNF296	Q8WUU4	11	NAN	NAN	NAN	22.04	22.77	23.03	22.98	23.09	NAN	NAN
ZNF318	Q5VUA4	9	NAN	NAN	NAN	NAN	20.69	20.53	20.18	20.65	NAN	NAN
ZNF319	Q9P2F9	4	NAN	NAN	NAN	20.21	20.01	20.53	20.35	19.09	NAN	20.41
ZNF326	Q5BKZ1	10	21.99	22.16	NAN	21.48	21.26	21.21	21.68	21.14	22.00	21.39
ZNF362	Q5T0B9	7	NAN	NAN	NAN	NAN	20.71	20.54	20.14	19.67	NAN	NAN
ZNF384	Q8TF68	13	20.94	21.88	22.72	23.17	24.12	25.03	23.73	23.86	22.52	22.87
ZNF462	Q96JM2	27	23.68	24.45	NAN	NAN	20.80	20.31	19.28	21.22	NAN	NAN
ZNF499	Q96K62	13	NAN	NAN	NAN	20.91	23.51	23.87	21.31	21.20	NAN	20.03
ZNF503	Q96F45	13	NAN	NAN	21.64	22.56	22.86	23.41	23.17	23.63	20.73	21.43
ZNF512	Q96ME7	14	NAN	NAN	NAN	NAN	22.50	22.36	22.22	21.44	22.16	22.03
ZNF512B	Q96KM6	10	NAN	NAN	NAN	NAN	21.85	21.38	20.66	20.06	NAN	NAN
ZNF516	Q92618	6	NAN	NAN	NAN	NAN	20.20	20.41	20.39	NAN	NAN	NAN
ZNF532	Q9HCE3	4	21.14	19.81	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
ZNF581	Q9P0T4	4	NAN	NAN	NAN	NAN	20.03	20.97	19.49	NAN	NAN	NAN

ZNF609	O15014	17	NAN	NAN	NAN	NAN	22.61	23.19	22.06	20.80	NAN	19.85
ZNF646	O15015	8	NAN	NAN	NAN	NAN	19.32	19.31	18.38	NAN	NAN	NAN
ZNF703	Q9H7S9	6	NAN	NAN	NAN	20.43	20.82	21.23	20.50	20.47	NAN	NAN
ZNF746	Q6NUN9	5	NAN	NAN	NAN	NAN	20.75	21.03	19.33	19.30	NAN	NAN
ZNF770	Q6IQ21	6	19.91	NAN	NAN	NAN	19.46	20.10	18.67	NAN	19.14	19.65
ZNF787	Q6DD87	6	NAN	NAN	NAN	NAN	20.31	20.88	20.44	19.60	19.72	19.72
ZNF827	Q17R98	4	NAN	NAN	NAN	NAN	20.26	21.77	21.39	20.85	NAN	NAN
ZNF865	P0CJ78	12	NAN	NAN	NAN	NAN	22.68	22.53	19.95	20.70	20.19	20.91
ZRANB2	O95218	12	NAN	NAN	NAN	21.85	22.51	22.41	22.46	21.99	22.57	22.59
ZYX	Q15942	7	NAN	NAN	NAN	NAN	NAN	NAN	20.55	19.86	20.89	20.84

Table 6.2 Identified Proteins SILAC and differential enrichment analysis

HF/hES_1	HF/hES_2	HF/hES_3	Signifi	Peptides	Log T-test p-value	T-test Diff	Genename	UniProtRev
1.42266	1.59053	1.5065	yes	13	2.98588	1.50656	ABCD3	P28288
1.05977	1.06833	1.14039	yes	6	3.25947	1.0895	ABCF2	Q9UG63
2.12257	2.03012	2.1681	yes	30	3.43066	2.10693	ACADVL	P49748
1.77678	NaN	1.62176	yes	12	1.53733	1.69927	ACOX1	Q15067
1.4328	1.6931	1.91926	yes	69	2.1604	1.68172	ACTN4	O43707
1.40218	0.883464	1.18796	yes	13	1.78312	1.15787	ACTR1A	P61163
0.864969	1.10125	1.44239	yes	8	1.67626	1.1362	ADAM9	Q13443
1.61027	1.59908	1.55528	yes	6	3.95236	1.58821	AFAP1	Q8N556
4.13824	3.45536	3.98687	yes	223	2.54288	3.86016	AHNAK	Q09666
3.64996	3.18487	3.66562	yes	22	2.6938	3.50015	ALCAM	Q13740
1.56423	1.76922	1.48151	yes	18	2.54867	1.60499	ALDH1B1	P30837
1.65265	1.28155	1.04124	yes	12	1.75601	1.32515	ALDH1L2	Q3SY69
2.01888	1.44821	1.73535	yes	10	2.05041	1.73415	ANO10	Q9NW15
5.78897	3.68437	3.53107	yes	39	1.5671	4.3348	ANPEP	P15144
1.20727	0.899717	1.20552	yes	32	2.07248	1.10417	ANXA2	P07355
1.16008	0.708408	1.45202	yes	12	1.44208	1.10684	AP1M1	Q9BXS5
1.63993	1.57119	1.61758	yes	37	3.80093	1.60957	AP2A1	O95782
1.1161	0.898015	1.06592	yes	47	2.38722	1.02668	AP2B1	P63010
1.44403	1.33988	1.38449	yes	19	3.3269	1.38947	AP2M1	Q96CW1
1.10621	1.16446	1.13862	yes	14	3.65798	1.13643	APMAP	Q9HDC9
1.37907	1.33165	1.37557	yes	6	3.90157	1.3621	ARF6	P62330
1.70306	1.18333	1.38482	yes	9	1.95452	1.42374	ARHGEF2	Q92974
1.31522	0.887213	1.48269	yes	12	1.69457	1.22837	ARPC1B	O15143
3.66857	2.93766	2.54693	yes	26	1.94274	3.05105	ASPH	Q12797
2.8125	3.47457	2.95786	yes	23	2.37439	3.08164	ATL3	Q6DD88
3.49902	3.01535	3.66721	yes	38	2.48176	3.39386	ATP2B4	P23634
2.72467	3.0616	NaN	yes	4	1.43147	2.89313	B2M	P61769
1.21257	1.4444	1.17409	yes	13	2.3623	1.27702	BCAP31	P51572
1.20814	1.27906	1.15218	yes	23	3.0388	1.21313	CALR	P27797
3.79223	3.82385	3.60987	yes	24	3.49836	3.74198	CALU	O43852
1.69095	1.017	1.58914	yes	8	1.6824	1.43236	CAMK2D	Q13557
2.05415	1.10601	1.77589	yes	14	1.55249	1.64535	CAPN2	P17655
2.04324	1.80896	2.35361	yes	12	2.23925	2.0686	CAV1	Q03135
4.08398	3.42761	3.50818	yes	30	2.50158	3.67326	CD109	Q6YHK3
3.46845	3.48736	3.40558	yes	11	4.29058	3.4538	CD44	P16070
3.68796	2.98162	3.86305	yes	5	2.23381	3.51088	CD59	P13987
1.90839	1.64741	1.71035	yes	3	2.69886	1.75538	CD63	P08962
1.2822	1.34051	1.44747	yes	4	2.89624	1.35673	CD81	P60033
3.02735	3.39451	2.68107	yes	8	2.33945	3.03431	CFL2	Q9Y281
0.974089	1.1562	0.977023	yes	5	2.47323	1.03577	CIRBP	Q14011
2.07608	2.01607	2.02137	yes	37	4.05265	2.03784	CKAP4	Q07065
1.3058	1.31168	1.51263	yes	8	2.61445	1.3767	CNP	P09543
1.78831	1.65246	1.7191	yes	48	3.28438	1.71996	COL12A1	Q99715
3.95726	2.90597	3.22517	yes	33	2.0729	3.3628	COL1A1	P02452
3.24236	3.14217	3.18856	yes	32	4.08466	3.19103	COL1A2	P08123
3.56998	3.27196	4.28695	yes	24	2.1852	3.70963	COL6A1	P12109
3.34028	2.49244	3.02595	yes	14	2.15803	2.95289	COL6A2	P12110
1.81959	2.94146	2.87434	yes	91	1.70395	2.54513	COL6A3	P12111
2.41616	2.05106	2.21017	yes	10	2.64841	2.2258	COLGALT1	Q8NBJ5
2.4493	2.81856	2.38612	yes	15	2.55561	2.55133	COMT	P21964
1.24799	1.21735	1.52396	yes	23	2.27304	1.32977	CORO1C	Q9ULV4
4.09609	3.86691	4.17608	yes	4	3.28079	4.04636	CRIP2	P52943
1.84358	1.86647	1.74537	yes	13	3.37991	1.81847	CRTAP	O75718
3.6828	3.96421	3.50195	yes	13	2.88369	3.71632	CRYAB	P02511
NaN	1.1167	1.1034	yes	8	2.41864	1.11005	CTBP1	Q13363
3.04315	2.15678	2.45217	yes	10	1.9882	2.5507	CTSA	P10619
4.63906	3.2878	3.45641	yes	14	1.90937	3.79442	CTSB	P07858
3.03466	2.88899	2.89468	yes	19	3.58082	2.93944	CYB5R3	P00387
2.74155	2.55046	3.04883	yes	17	2.56623	2.78028	DAB2	P98082
1.33594	1.01628	1.09484	yes	28	2.15909	1.14902	DCTN1	Q14203
1.66084	1.77594	1.48393	yes	6	2.5735	1.64024	DECR1	Q16698
1.65892	1.83374	1.19182	yes	24	1.83195	1.56149	DNAJC13	O75165
1.94565	2.02343	NaN	yes	8	1.904	1.98454	ECE1	P42892
1.62989	1.74687	1.47933	yes	17	2.64195	1.6187	ECI2	O75521
3.14117	3.47962	3.9631	yes	26	2.34304	3.52796	EHD2	Q9NZN3
2.3147	2.54809	2.61181	yes	4	2.88232	2.49153	ELOVL1	Q9BW60
1.22645	2.0121	1.78425	yes	12	1.724	1.67427	EMD	P50402
2.42715	1.36642	1.31777	yes	13	1.37376	1.70378	ERBB2IP	Q96RT1
1.89185	2.36457	2.21785	yes	9	2.38049	2.15809	ERGIC1	Q969X5
1.04488	0.974676	NaN	yes	6	1.65519	1.00978	ERLEC1	Q96DZ1
1.78211	1.56311	1.59077	yes	14	2.75778	1.64533	ERLIN1	O75477
2.09855	2.00906	1.80715	yes	16	2.72005	1.97159	ERO1L	Q96HE7
2.76477	2.37887	2.82028	yes	19	2.56493	2.65464	ESYT2	A0FGR8
1.73829	1.58919	1.58275	yes	12	3.01674	1.63674	ETFA	P13804
1.55208	1.48342	1.3514	yes	12	2.7911	1.4623	ETFB	P38117
1.67978	1.30422	1.61829	yes	3	2.24426	1.5341	FAHD1	Q6P587

0.836813	1.28913	1.49523	yes	18	1.60236	1.20706	FAM120A	Q9NZB2
2.83402	2.43095	3.03164	yes	23	2.39148	2.76554	FAM129B	Q96TA1
1.14522	1.56511	1.26592	yes	13	2.05794	1.32542	FARP1	Q9Y4F1
3.18558	2.23701	2.86882	yes	21	1.99894	2.7638	FBLN2	P98095
2.57007	2.1845	2.17916	yes	18	2.50571	2.31124	FHL2	Q14192
2.1845	2.13606	2.45512	yes	26	2.71528	2.25856	FKBP10	Q96AY3
1.6658	1.83596	1.76952	yes	3	3.10068	1.75709	FKBP11	Q9NYL4
1.40037	1.75519	1.49769	yes	3	2.33491	1.55108	FKBP2	P26885
3.4957	2.70131	3.24041	yes	16	2.26007	3.14581	FKBP9	O95302
1.17773	0.95017	1.17133	yes	29	2.33767	1.09974	FLII	Q13045
1.22602	0.799336	1.22039	yes	141	1.77905	1.08192	FLNA	P21333
1.79847	0.933799	1.70266	yes	146	1.48677	1.47831	FLNC	Q14315
5.61291	5.014	5.27534	yes	103	2.97149	5.30075	FN1	P02751
1.67016	1.09038	1.34142	yes	15	1.83149	1.36732	FNDC3B	Q53EP0
1.12174	0.822852	1.40996	yes	4	1.65339	1.11818	FTL	P02792
1.64492	0.975557	1.15523	yes	14	1.6137	1.25857	G6PD	P11413
1.75039	2.13596	2.32328	yes	9	2.18223	2.06988	GBA	P04062
3.12408	2.21801	2.18739	yes	18	1.83392	2.50983	GBE1	Q04446
1.47659	1.04089	1.29443	yes	21	2.01136	1.27064	GBF1	Q92538
1.49477	1.18447	1.2225	yes	9	2.25202	1.30058	GLB1	P16278
1.50213	1.87778	1.59364	yes	23	2.33523	1.65785	GLS	O94925
1.77227	1.38973	0.888695	yes	13	1.46757	1.35023	GNA11	P29992
1.1141	1.21952	1.30001	yes	15	2.7057	1.21121	GNAS	O95467
1.41841	1.65434	1.68383	yes	6	2.55371	1.58553	GNG12	Q9UBI6
1.35991	1.10909	0.738206	yes	9	1.56278	1.06907	GNS	P15586
1.60103	1.73946	1.17983	yes	11	1.91204	1.50677	GOLIM4	O00461
3.3069	4.35304	3.98222	yes	12	2.20976	3.88072	GPC1	P35052
2.26475	2.46543	2.26261	yes	15	3.08018	2.33093	GSN	P06396
2.24577	2.2578	1.58294	yes	5	1.92576	2.02884	GSTK1	Q9Y2Q3
2.42108	2.72395	NaN	yes	5	1.42675	2.57252	H1F0	P07305
1.53247	1.20995	1.36244	yes	12	2.337	1.36829	H2AFY	O75367
1.25972	1.18732	1.20232	yes	14	3.4831	1.21645	HADHB	P55084
1.44223	1.49447	1.58818	yes	40	3.09673	1.50829	HDLBP	Q00341
1.31968	1.03196	1.47773	yes	8	1.98763	1.27646	HEXB	P07686
1.10615	NaN	1.12552	yes	9	2.25763	1.11584	HIST1H1E	P10412
2.21356	2.75967	2.57492	yes	14	2.39381	2.51605	HLA-A	P01891
2.2131	1.58559	1.57884	yes	6	1.87008	1.79251	HM13	Q8TCT9
2.73583	2.22722	2.42167	yes	13	2.44324	2.46157	HMOX1	P09601
0.947853	1.19912	1.10313	yes	23	2.34344	1.08337	HNRNPUL2	Q1KMD3
2.78088	2.71644	1.88955	yes	13	1.87574	2.46229	HP1BP3	Q5SSJ5
1.89313	1.14835	1.62784	yes	14	1.72013	1.55644	HSPB1	P04792
2.87527	2.60279	2.41622	yes	55	2.59247	2.63143	HSPH1	Q92598
2.02382	1.97493	1.87129	yes	19	3.27759	1.95668	IDH2	P48735
1.24147	0.953228	1.08651	yes	13	2.24043	1.09374	IKBIP	Q70UQ0
1.42299	1.90095	1.90203	yes	10	2.08199	1.74199	IKBIP	Q70UQ0
1.1121	0.790105	1.1501	yes	11	1.90785	1.01743	ILK	Q13418
1.43819	1.65526	1.37579	yes	6	2.49261	1.48975	IMPAD1	Q9NX62
2.87784	2.13836	1.75116	yes	19	1.68197	2.25579	INF2	Q27J81
1.0966	0.857344	1.20226	yes	84	2.03272	1.05207	IQGAP1	P46940
2.20267	2.46009	2.287	yes	14	2.97141	2.31659	ITGA3	P26006
2.58251	1.92809	2.00526	yes	19	2.04977	2.17195	ITGA5	P08648
1.34307	1.29872	1.46415	yes	29	2.88531	1.36865	ITGB1	P05556
2.32048	2.16989	2.21863	yes	9	3.40527	2.23633	KDELC2	Q7Z4H8
0.882134	1.22534	1.07011	yes	1	2.06238	1.05919	KRTCAP2	Q8N6L1
1.41576	1.35168	1.39226	yes	8	3.73957	1.38657	LAMP1	P11279
1.0943	1.81709	1.8431	yes	5	1.63557	1.58483	LAMP2	P13473
1.89848	1.32377	1.67956	yes	21	1.9854	1.63394	LDHA	P00338
2.24132	2.05304	2.3364	yes	15	2.84893	2.21025	LEPREL2	Q8IVL6
3.40531	2.97878	3.21406	yes	10	2.82884	3.19938	LGALS1	P09382
1.10091	1.05262	1.04691	yes	14	3.58894	1.06681	LMAN1	P49257
4.41799	3.88762	4.32128	yes	55	2.82453	4.20896	LMNA	P02545
3.43243	3.19128	4.57996	yes	58	1.88926	3.73456	LMO7	Q8WWI1
1.65576	1.96761	1.78831	yes	80	2.6021	1.80389	LRP1	Q07954
1.56793	1.54646	1.56647	yes	16	4.70544	1.56029	LRRC59	Q96AG4
1.33142	0.970044	1.2112	yes	9	2.0897	1.17089	LRRFIP1	Q32MZ4
1.32152	1.32671	1.0859	yes	6	2.39293	1.24471	MANF	P55145
NaN	3.24047	3.29256	yes	18	2.29449	3.26652	MAP1A	P78559
1.53107	0.898247	1.4863	yes	86	1.62812	1.30521	MAP1B	P46821
1.31927	1.29331	1.09275	yes	6	2.47609	1.23511	MARCKS	P29966
2.14783	1.82509	1.86005	yes	18	2.55999	1.94432	MFGE8	Q08431
1.27041	1.14084	1.1877	yes	7	3.00199	1.19965	MGST3	O14880
1.21481	1.05769	1.73057	yes	11	1.64936	1.33436	MMP14	P50281
NaN	2.1311	2.2502	yes	10	1.76192	2.19065	MOXD1	Q6UVY6
3.42962	2.61558	3.0968	yes	35	2.22484	3.04733	MRC2	Q9UBG0
1.37446	1.0708	1.29378	yes	46	2.27844	1.24635	MSN	P26038
1.59732	1.50238	0.983094	yes	10	1.71867	1.36093	MTDH	Q86UE4
3.38142	3.49812	3.05728	yes	40	2.80098	3.31227	MVP	Q14764
1.92907	2.80983	2.7096	yes	3	1.90869	2.48283	MYDGF	Q969H8
1.24001	0.542109	1.23707	yes	175	1.3071	1.0064	MYH9	P35579

1.65402	1.45801	1.58861	yes	12	2.86985	1.56688	MYO1B	O43795
2.45033	2.05679	2.29769	yes	45	2.59503	2.26827	MYO1C	O00159
3.19104	3.02217	3.53506	yes	97	2.66759	3.24942	MYOF	Q9NZM1
1.07738	0.943209	1.10996	yes	6	2.62294	1.04352	NANS	Q9NR45
3.92391	3.23619	2.86213	yes	11	2.06794	3.34074	NCEH1	Q6PIU2
3.05625	2.33685	1.6663	yes	8	1.55476	2.35313	NEK7	Q8TDX7
2.39383	1.99143	1.81791	yes	6	2.17156	2.06772	NIPSNAP3A	Q9UFN0
1.98732	2.11043	1.93621	yes	14	3.18033	2.01132	NNT	Q13423
1.41115	1.13632	1.74846	yes	12	1.82566	1.43198	NPC1	O15118
1.70182	2.04558	1.95736	yes	4	2.5338	1.90159	NPTN	Q9Y639
1.51974	1.98251	1.24823	yes	18	1.74872	1.58349	NSF	P46459
5.426	5.32589	5.72438	yes	26	3.3237	5.49209	NT5E	P21589
2.10212	2.52103	2.50238	yes	9	2.48242	2.37518	NUCB2	P80303
1.12459	1.02694	0.857503	yes	49	2.22207	1.00301	NUMA1	Q14980
1.18701	1.20714	1.03823	yes	27	2.66545	1.14413	OGDH	Q02218
1.89325	1.72312	0.971884	yes	10	1.48694	1.52942	OSBPL3	Q9H4L5
2.60711	2.60628	2.4283	yes	26	3.26396	2.54723	P4HA1	P13674
4.27008	3.71083	3.34823	yes	17	2.30074	3.77638	P4HA2	O15460
2.23695	2.09004	2.16553	yes	43	3.4158	2.16417	P4HB	P07237
1.15536	1.15108	1.50223	yes	6	2.08125	1.26956	PARVA	Q9NVD7
1.55075	1.90064	1.62691	yes	15	2.4072	1.69277	PCYOX1	Q9UHG3
1.89231	1.70186	1.80385	yes	18	3.02972	1.79934	PDLIM7	Q9NR12
1.39523	1.35671	1.38394	yes	19	4.16264	1.37863	PICALM	Q13492
1.9492	1.56487	1.64289	yes	24	2.33505	1.71899	PITRM1	Q5JRX3
2.9735	2.72312	3.03385	yes	274	2.97192	2.91016	PLEC	Q15149
2.49226	2.91209	2.73327	yes	26	2.69793	2.71254	PLOD1	Q02809
2.32987	2.15779	2.39023	yes	21	3.03561	2.29263	PLOD2	O00469
2.20376	2.24607	2.02606	yes	22	3.01166	2.15863	PLOD3	O60568
1.47415	1.34721	1.72953	yes	5	2.2638	1.51696	POFUT1	Q9H488
NaN	2.60466	2.58513	yes	4	2.62057	2.5949	PPAP2B	O14495
1.79539	1.21083	1.62887	yes	11	1.90555	1.54503	PPFIBP1	Q86W92
1.38305	1.34806	1.42514	yes	14	3.5874	1.38542	PPIB	P23284
1.4453	1.41099	1.37868	yes	9	3.73142	1.41166	PRKACA	P17612
3.85619	2.12005	2.604	yes	7	1.506	2.86008	PRKACA	P17252
2.1173	1.73695	1.97596	yes	10	2.48862	1.9434	PRKAR1A	P10644
2.11673	2.27304	2.81574	yes	5	2.11421	2.40184	PRKCDBP	Q969G5
0.938323	1.20239	1.13934	yes	22	2.27889	1.09335	PTK7	Q13308
3.17714	2.69797	3.27253	yes	14	2.47088	3.04921	PTRF	Q6NZI2
0.91127	1.11317	1.40218	yes	2	1.81812	1.14221	PTTG1IP	P53801
1.43749	1.2969	1.94107	yes	31	1.813	1.55849	PYGB	P11216
1.42551	1.54473	1.37535	yes	16	2.92067	1.44853	RAB14	P61106
1.08929	1.28291	1.21064	yes	13	2.65174	1.19428	RAB2	P61019
2.67399	2.70119	2.79165	yes	8	3.76795	2.72228	RAB3B	P20337
1.22169	0.924404	1.20696	yes	10	2.13033	1.11768	RAB5C	P51148
1.06261	0.975924	0.962068	yes	15	3.0053	1.0002	RAB7A	P51149
1.66776	2.06568	1.569	yes	19	2.13693	1.76748	RAI14	Q9P0K7
1.33268	1.50833	1.48774	yes	16	2.83183	1.44292	RAP1B	P61224
1.28327	1.13704	1.30439	yes	19	2.74684	1.24157	RCN1	Q15293
1.42659	1.66653	1.68415	yes	3	2.56697	1.59242	RER1	O15258
1.95375	1.56686	2.93569	yes	11	1.46829	2.1521	RFTN1	Q14699
1.84699	1.53968	2.17444	yes	19	2.01621	1.8537	RNH1	O60930
5.23281	4.55391	5.00342	yes	7	2.78738	4.93005	RPL14	P50914
1.04299	1.07594	0.933648	yes	31	2.74923	1.01753	RPN1	P04843
2.32579	3.12153	2.47207	yes	8	2.07199	2.6398	RRAS	P10301
1.66993	1.73223	1.6597	yes	65	3.74379	1.68729	RRBP1	Q9P2E9
1.64533	1.54587	1.6089	yes	14	3.48212	1.60003	RTN4	Q9NQC3
4.27068	3.37615	3.92458	yes	3	2.34413	3.85714	S100A6	P06703
2.3691	2.38006	2.06533	yes	13	2.68718	2.2715	SCARB2	Q14108
1.91112	1.29048	1.70097	yes	9	1.91329	1.63419	SCCPDH	Q8NBX0
1.67487	2.06361	1.4518	yes	8	1.97849	1.73009	SCP2	O14595
0.780814	1.33297	1.04852	yes	5	1.65529	1.0541	SDF2	Q99470
1.66084	2.03569	1.80587	yes	4	2.45328	1.83413	SEC22B	O75396
1.9539	2.12578	2.086	yes	13	3.19499	2.05523	SEC22B	O75396
1.53973	1.32953	1.42546	yes	28	2.74561	1.43157	SEC23A	Q15436
1.22946	1.61245	1.49667	yes	12	2.21518	1.44619	SEC24D	O94855
1.25133	1.0497	1.25936	yes	11	2.47843	1.1868	SEC61A1	P61619
1.48862	1.35688	NaN	yes	10	1.53087	1.42275	SEL1L	Q9UBV2
1.35581	1.12935	1.47643	yes	13	2.23041	1.32053	Sep-11	Q9NVA2
2.30547	1.83649	1.9813	yes	8	2.33891	2.04109	SERPINE1	P05121
1.65608	1.31075	1.95877	yes	10	1.89442	1.64187	SH3BP4	Q9P0V3
2.93452	4.61105	4.12895	yes	9	1.79574	3.89151	SLC1A5	Q15758
1.76702	1.78676	1.3634	yes	5	2.15435	1.63906	SLC38A2	Q96QD8
1.76859	1.38278	1.78396	yes	9	2.20038	1.64511	SLC7A1	P30825
1.5007	1.25629	1.10969	yes	10	2.11134	1.28889	SMARCC2	Q8TAQ2
1.21829	0.954345	1.11343	yes	11	2.31238	1.09535	SNX9	Q9Y5X1
1.1447	1.22725	0.915406	yes	4	2.14452	1.09579	SOD2	P04179
1.46587	1.84611	1.35795	yes	14	2.04942	1.55664	SRPR	P08240
1.24367	1.44424	1.37579	yes	13	2.72513	1.35457	SRPRB	Q9Y5M8
4.26123	4.20469	3.41278	yes	11	2.32328	3.95957	STOM	P27105

0.947255	1.06488	1.04872	yes	18	2.88632	1.02029	STT3A	P46977
1.07772	1.29243	0.98156	yes	14	2.17414	1.11724	STT3B	Q8TCJ2
1.37857	1.27453	1.16755	yes	8	2.64203	1.27355	STX12	Q86Y82
1.6532	1.98907	2.71339	yes	10	1.67541	2.11855	SUCLG2	Q96I99
3.18967	2.55255	1.96584	yes	20	1.73526	2.56935	SUN2	Q9UH99
2.15196	1.90612	2.0191	yes	7	2.91089	2.02573	TBL2	Q9Y4P3
NaN	1.55105	1.75587	yes	3	1.40473	1.65346	TEAD1	P28347
1.24951	1.26303	1.07608	yes	10	2.59821	1.19621	TLDC1	Q6P9B6
2.0256	1.55243	2.01228	yes	126	2.1614	1.86344	TLN1	Q9Y490
1.43301	1.57681	1.70783	yes	14	2.59564	1.57255	TMEM214	Q6NUQ4
2.1398	1.9185	2.10852	yes	19	2.94709	2.05561	TMEM43	Q9BTV4
2.20135	2.00899	2.22639	yes	8	2.99016	2.14558	TMX3	Q96JJ7
2.09322	1.45828	3.17239	yes	24	1.33355	2.2413	TOMM20	Q15388
2.09217	1.8	2.31803	yes	36	2.28348	2.07007	TPM1	P09493
2.42121	2.55766	2.23863	yes	6	2.83199	2.40583	TRAM2	Q15035
1.40844	1.45775	1.55812	yes	14	3.05036	1.47477	TRIM25	Q14258
1.7015	1.53933	1.56613	yes	17	3.00891	1.60232	TXNDC5	Q8NBS9
2.57606	2.05592	2.23441	yes	12	2.35502	2.2888	UAP1	Q16222
2.09376	1.72979	1.99237	yes	23	2.50657	1.93864	UGDH	O60701
3.47599	3.02489	3.53767	yes	70	2.63357	3.34618	VIM	P08670
1.4984	0.834064	1.17204	yes	8	1.58651	1.16817	WFS1	O76024
2.13763	1.57206	1.86568	yes	9	2.1173	1.85846	FAM114A1	Q8IWE2
1.40076	1.86386	1.69381	yes	20	2.17852	1.65281	P3H1	Q32P28
-1.68548	-1.94197	-1.82623	yes	38	2.77989	-1.81789	AARS	P49588
-2.40645	-2.70237	-2.36982	yes	25	2.74989	-2.49288	AASS	Q9UDR5
-3.32063	-3.12608	NaN	yes	4	1.71656	-3.22336	ABRACL	Q9P1F3
-2.04579	-2.43792	-2.00613	yes	10	2.39438	-2.16328	ACAT2	Q9BWD1
-1.30465	-1.78996	-1.10628	yes	9	1.69058	-1.4003	ACOT7	O00154
-2.10569	-1.99286	-1.84492	yes	22	2.83883	-1.98116	ADFP	Q99541
-1.08061	-1.47361	-1.2285	yes	7	2.08833	-1.26091	ADH5	P11766
-1.6486	-1.92309	-1.78289	yes	9	2.70655	-1.78486	ADSL	P30566
-1.64598	-1.81284	-1.82414	yes	12	2.97143	-1.76099	ADSS	P30520
-1.0949	NaN	-1.22482	yes	14	1.44833	-1.15986	AFG3L2	Q9Y4W6
-1.99798	-2.32402	-1.85481	yes	13	2.34523	-2.05894	AHCY	P23526
NaN	-1.2224	-1.25508	yes	7	2.07587	-1.23874	AHSA1	O95433
-1.71378	-2.31315	-2.06431	yes	10	2.13956	-2.03041	AK4	P27144
-0.91001	-1.7574	-1.52807	yes	9	1.50561	-1.39849	AKR1A1	P14550
-0.89183	-1.38048	-1.00058	yes	7	1.74618	-1.09096	AKR1B1	P15121
-2.03635	-1.87535	-1.60753	yes	13	2.33825	-1.83974	ALDH2	P05091
-1.49537	-1.26732	-1.54406	yes	15	2.45447	-1.43558	ALDH3A2	P51648
-0.84285	-1.14321	-1.0185	yes	19	2.12598	-1.00152	ALDH7A1	P49419
-2.20124	-4.23107	-2.67567	yes	19	1.41525	-3.03599	ANXA3	P12429
-1.21083	-1.21998	-1.16884	yes	14	3.76412	-1.19988	APEH	P13798
-1.54612	-1.44788	-1.59379	yes	20	3.10344	-1.52926	APP	P05067
-1.56281	NaN	-1.79196	yes	5	1.36234	-1.67738	ARFGAP2	Q8N6H7
-2.16838	-2.39935	-2.43643	yes	18	2.89024	-2.33472	ASNS	P08243
-1.65222	-2.40408	-2.01905	yes	29	1.94713	-2.02512	ATIC	P31939
-1.19525	-1.36053	NaN	yes	9	1.38603	-1.27789	BZW2	Q9Y6E2
-1.11307	-0.9792	-1.19575	yes	6	2.48184	-1.09601	C1QBP	Q07021
-1.22119	-1.32822	-1.17547	yes	50	2.87735	-1.24163	CAD	O76075
-0.9718	-1.23216	-0.95364	yes	35	2.14103	-1.05253	CAND1	Q86VP6
-1.36792	-2.20656	-1.81472	yes	12	1.75187	-1.7964	CAPG	P40121
-2.74623	-2.4412	-2.09752	yes	13	2.22904	-2.42832	CASP3	P42574
-1.05919	-1.21957	-1.06389	yes	8	2.65187	-1.11422	CBX5	P45973
-1.48645	-1.91664	-1.60573	yes	5	2.2331	-1.66961	CD2AP	Q9Y5K6
-1.37494	-1.83357	-1.80692	yes	11	2.10725	-1.67181	CDK1	P06493
-1.32847	-1.2412	-1.09854	yes	16	2.52429	-1.22274	CEBPZ	Q03701
-1.60301	-1.88769	-1.36268	yes	6	2.06135	-1.61779	CHORDC1	Q9UHD1
-1.63671	-1.92489	-1.4933	yes	14	2.24991	-1.68497	CKB	P12277
-2.08009	-3.26202	-2.38934	yes	24	1.73664	-2.57715	CNDP2	Q96KP4
-1.14976	NaN	-1.2059	yes	8	1.81904	-1.17783	COTL1	Q14019
-1.42171	-2.56124	-3.22769	yes	9	1.34768	-2.40355	CRABP1	P29762
-1.21736	-1.97132	-1.90622	yes	11	1.70817	-1.6983	CSDA	P16989
-1.16809	-1.27415	-1.26618	yes	42	3.11905	-1.23614	CSE1L	P55060
-1.4231	-2.25099	-1.62999	yes	9	1.71609	-1.76803	CSRP2	Q16527
-2.11572	-2.48261	-2.60735	yes	9	2.42569	-2.40189	CTSC	P53634
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-1.60942	NaN	-1.59732	yes	3	2.6194	-1.60337	DDT	P30046
-1.15056	-0.95741	-1.27509	yes	5	2.17723	-1.12769	DDX52	Q9Y2R4
-1.33232	-1.08259	-1.3054	yes	10	2.39278	-1.2401	DHCR24	Q15392
-0.93066	-1.13046	-1.06079	yes	11	2.50156	-1.04063	DNAJA2	O60884
-4.15889	-2.90703	-3.09764	yes	21	1.88751	-3.38785	DNMT3A	Q9Y6K1
-3.38683	-2.80037	-3.61823	yes	35	2.25965	-3.26848	DNMT3B	Q9UBC3
-1.64165	NaN	-1.6385	yes	6	3.21371	-1.64007	DPPA4	Q7L190
-2.26216	-2.67927	-2.40331	yes	26	2.60315	-2.44825	DPYSL3	Q14195
-1.29396	-1.41758	-1.20946	yes	33	2.67141	-1.307	ECM29	Q5VYK3
-1.25677	-1.13074	-1.26896	yes	11	2.88225	-1.21882	EIF4B	P23588
-1.48185	-1.69507	-1.52118	yes	39	2.75813	-1.56603	EZR	P15311

-3.74346	-3.78958	-3.53977	yes	14	3.36443	-3.69094	FABP5	Q01469
-2.34249	-1.95607	-2.29039	yes	7	2.51935	-2.19632	FADS2	O95864
-1.52272	-1.22337	-1.0147	yes	10	1.86805	-1.2536	FAR1	Q8WVX9
-1.25336	-1.72619	-1.28571	yes	90	1.9465	-1.42175	FASN	P49327
-2.55376	-2.37415	-2.46801	yes	20	3.35426	-2.46531	FDFT1	P37268
-2.82409	-3.04716	-2.717	yes	25	2.93854	-2.86275	FKBP4	Q02790
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-1.58225	-1.55152	-1.69404	yes	9	3.14069	-1.60927	GALNT7	Q86SF2
-2.15117	-2.14388	-1.93821	yes	26	2.94817	-2.07775	GART	P22102
-0.84601	-1.37464	-1.11832	yes	30	1.73778	-1.11299	GDI2	P50395
-0.83524	-1.36264	-0.97628	yes	26	1.66784	-1.05805	GFPT1	Q06210
-1.21846	-1.81553	-1.31775	yes	15	1.8005	-1.45058	GFPT2	O94808
-2.74642	-2.49761	-2.37617	yes	15	2.73628	-2.54007	GJA1	P17302
-3.94326	-3.2105	-2.66456	yes	23	1.90065	-3.27277	GLDC	P23378
-1.59571	-2.31115	-1.70237	yes	8	1.85671	-1.86974	GLO1	Q04760
-1.17873	-2.08345	-1.58135	yes	11	1.5972	-1.61451	GLRX3	O76003
-1.41812	-1.88092	-1.53772	yes	11	2.13551	-1.61225	GOT1	P17174
-2.90142	-2.99551	-2.64629	yes	16	2.87311	-2.84774	GPC4	O75487
-2.2133	-3.17762	-2.44796	yes	12	1.9164	-2.61296	GSTP1	P09211
-1.32869	-2.01019	-1.59872	yes	3	1.84817	-1.64587	HINT1	P49773
-1.41001	-1.56222	-1.37165	yes	3	2.79282	-1.44796	HMGA1	P17096
-2.2051	-1.82235	-1.49281	yes	14	1.91079	-1.84009	HMGCS1	Q01581
-1.49058	-1.89749	-1.56499	yes	54	2.24476	-1.65102	HSP90AB1	P08238
-1.50226	-1.94442	-1.67853	yes	11	2.25096	-1.7084	HSP90AB2P	Q58FF8
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-1.83341	-1.78121	-1.85914	yes	44	3.80181	-1.82459	HSPD1	P10809
-1.4385	-1.41565	-1.49513	yes	6	3.57604	-1.44976	HSPG2	P98160
-3.29945	-3.05841	-3.30173	yes	17	3.20202	-3.21986	IDH1	O75874
-2.95456	-3.57316	-3.78819	yes	21	2.28076	-3.43864	IGF2BP1	Q9NZI8
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-1.21669	-1.3407	NaN	yes	12	1.5108	-1.27869	IPO9	Q96P70
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-2.24797	-2.57355	-2.44938	yes	18	2.81572	-2.42363	KPNA2	P52292
-4.11299	-3.71867	-3.14573	yes	32	2.23376	-3.65913	KRT18	P05783
-2.09486	-2.64232	-2.68205	yes	40	2.23526	-2.47308	L1TD1	Q5T7N2
-0.99821	-1.30632	-0.98542	yes	33	2.04449	-1.09665	LARS	Q9P2J5
-1.35258	-1.57824	-1.38255	yes	8	2.61744	-1.43779	LBR	Q14739
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-2.24264	-2.7818	-2.44717	yes	19	2.40257	-2.49054	LDHB	P07195
-3.79684	-3.45109	-4.00518	yes	14	2.73272	-3.75104	LIN28A	Q9H9Z2
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-0.99536	-1.44136	-1.21307	yes	12	1.95795	-1.2166	MAGED2	Q9UNF1
-1.22695	-1.11594	-1.2127	yes	24	3.06319	-1.1852	MAN2A1	Q16706
-0.97361	-1.04802	-1.09237	yes	22	2.95379	-1.038	MARS	P56192
-1.75239	-1.49977	-1.28265	yes	12	2.09873	-1.5116	MCAM	P43121
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-2.35078	-2.77369	-2.00451	yes	96	2.06316	-2.37633	MDN1	Q9NU22
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-1.29396	-1.37737	-1.33214	yes	5	3.48655	-1.33449	MSMO1	Q15800
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-1.00468	-1.19021	-1.08418	yes	5	2.61823	-1.09302	NACA	E9PAV3
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-1.11923	-1.73629	-1.16459	yes	6	1.67248	-1.34004	PITPNB	P48739
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-1.41577	-1.59697	-1.40167	yes	10	2.73964	-1.47147	SET	Q01105
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-2.16566	-2.17377	-2.28335	yes	20	3.52959	-2.20759	SLC25A24	Q6NUK1
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0.348686	0.440314	0.220701	no	16	1.46865	0.336567	ACAA2	P42765
1.07834	0.900104	0.923339	no	13	2.47777	0.967261	ACAT1	P24752
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0.599794	0.243669	0.461109	no	10	1.28085	0.434857	AHCYL1	O43865
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0.272262	-0.07341	0.263996	no	47	0.511169	0.154283	ANXA6	P08133
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0.249749	0.170694	0.065159	no	15	1.02694	0.161867	AP1G1	O43747
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0.227618	0.06874	0.309293	no	11	0.984262	0.201884	AP3D1	O14617
0.194591	0.080794	0.263275	no	6	1.10944	0.179553	AP3M1	Q9Y2T2
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0.738984	0.215492	1.00065	no	5	0.975158	0.651709	ARPC5	O15511
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0.197362	0.411209	0.460585	no	19	1.32123	0.356385	ATAD3A	Q9NVI7
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0.532367	0.693855	0.69323	no	12	2.15632	0.639817	ATP13A1	Q9HD20
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0.255561	0.437121	0.246469	no	40	1.42992	0.31305	ATP2A2	P16615
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1.20044	0.53057	1.4461	no	6	1.21666	1.05904	NEXN	Q0ZGT2
3.72279	1.6602	3.92343	no	11	1.29846	3.10214	NQO1	P15559
1.69019	-0.03423	1.53077	no	12	0.713858	1.06224	NRP1	O14786
1.60815	0.983532	NaN	no	14	0.822291	1.29584	PLXNB2	O15031
2.66403	NaN	1.6683	no	6	0.842177	2.16617	PTGIS	Q16647
2.11912	NaN	1.66093	no	5	1.11469	1.89002	RAB23	Q9ULC3
1.14183	1.4282	NaN	no	4	1.15092	1.28501	RBM3	P98179
3.85868	2.73747	NaN	no	15	0.969855	3.29807	RCN3	Q96D15
NaN	2.02963	2.9181	no	11	0.946487	2.47387	RHOC	P08134
NaN	1.46801	1.87421	no	6	1.11354	1.67111	RHOG	P84095
0.125519	1.11597	3.8055	no	14	0.57576	1.68233	SLC25A1	P53007
1.22002	0.996967	NaN	no	4	1.19493	1.10849	SLC3A2	P08195
NaN	1.61504	1.1173	no	8	0.940388	1.36617	SPARC	P09486
3.67061	1.33862	NaN	no	9	0.556932	2.50461	SQRDL	Q9Y6N5
2.70383	3.44798	0.661202	no	21	0.949469	2.271	SYNE1	Q8NF91
2.75363	3.66221	NaN	no	9	1.04789	3.20792	SYNPO2	Q9UMS6
NaN	1.21996	1.51672	no	12	1.16263	1.36834	TPD52L2	O43399
NaN	1.66125	0.770787	no	5	0.650838	1.21602	TRAM1	Q15629
NaN	1.92509	1.16169	no	6	0.811502	1.54339	DDR2	Q16832
NaN	-1.20201	-0.8636	no	17	0.985565	-1.0328	ACACA	Q13085
NaN	-2.79796	-1.91828	no	7	0.930353	-2.35812	APRT	P07741
-1.37236	-2.7539	NaN	no	7	0.686803	-2.06313	ARMT1	Q9H993
-3.71698	-4.48691	NaN	no	12	1.22496	-4.10194	BCAT1	P54687
NaN	-1.37494	-2.05757	no	4	0.903176	-1.71626	CD9	P21926
NaN	-0.76444	-1.61158	no	6	0.661479	-1.18801	DHCR7	Q9UBM7
-0.9979	-1.24581	NaN	no	19	1.15454	-1.12185	DSG2	Q14126
-1.26143	-1.45593	-0.52406	no	10	1.20349	-1.08047	EIF4H	Q15056
-2.67328	NaN	-3.8017	no	9	0.959227	-3.23749	EPCAM	P16422
-3.55947	-2.13924	NaN	no	42	0.808296	-2.84935	EPPK1	P58107
-0.64323	-1.43803	NaN	no	8	0.634071	-1.04063	EPS8L2	Q9H6S3
NaN	-2.49322	-4.17546	no	10	0.803239	-3.33434	F11R	Q9Y624
-0.85909	-1.78195	NaN	no	8	0.669565	-1.32052	FAM49B	Q9NUQ9
NaN	-1.26979	-1.00526	no	6	1.13258	-1.13753	FDPS	P14324
-0.58888	-2.04168	-2.59903	no	5	0.997297	-1.7432	FIP1L1	Q6UN15
-1.10426	-1.7324	NaN	no	4	0.857823	-1.41833	GMFB	P60983
-1.40924	-1.07643	NaN	no	8	1.07194	-1.24283	HELLS	Q9NRZ9
-2.8626	NaN	-2.16385	no	25	1.05583	-2.51323	JUP	P14923
-3.85895	-1.68659	-2.45593	no	5	1.2805	-2.66716	METTL7A	Q9H8H3
-1.53642	-1.95148	NaN	no	9	1.12261	-1.74395	NOLC1	Q14978
-1.58199	-2.00857	-0.75614	no	7	1.23093	-1.4489	NUDT5	Q9UKK9
-0.64449	-1.64693	-1.57915	no	4	1.24047	-1.29019	NUTF2	P61970
-1.74458	-2.2051	NaN	no	8	1.13139	-1.97484	OCLN	Q16625
-0.70595	-1.81777	-1.47265	no	12	1.25344	-1.33212	PAK1	Q13153
NaN	-1.55962	-1.88262	no	4	1.22503	-1.72112	PHP14	Q9NRX4
NaN	-1.84477	-1.34132	no	10	1.001	-1.59304	PLD3	Q8IV08
NaN	-0.84858	-1.4231	no	8	0.802177	-1.13584	POU5F1	Q01860
-1.15602	-1.94792	-0.85831	no	10	1.25492	-1.32075	PPA1	Q15181
-1.85157	-1.19021	NaN	no	6	0.865517	-1.52089	PPAT	Q06203
-0.99746	-1.17853	NaN	no	11	1.27694	-1.088	PPM2C	Q9P0J1
-3.88483	NaN	-2.10079	no	11	0.734215	-2.99281	PTBP2	Q9UKA9
NaN	-1.05242	-1.46196	no	6	0.988052	-1.25719	RBPMS	Q93062
-2.60639	-1.77443	NaN	no	4	0.922714	-2.19041	RRM2B	Q7LG56
-0.35117	NaN	-2.09376	no	4	0.404272	-1.22246	SCD	O00767

-1.73836	NaN	-1.13758	no	18	0.882385	-1.43797	SEC23B	Q15437
-1.73322	-2.30707	NaN	no	11	1.04663	-2.02014	SEPHS1	P49903
-1.43788	-1.7826	-0.65488	no	9	1.21683	-1.29179	STK26	Q9P289
-1.94964	-2.51672	NaN	no	4	1.09475	-2.23318	TBCA	O75347
-1.60021	-1.20141	NaN	no	7	1.04568	-1.40081	TFAM	Q00059
-1.41935	NaN	-1.17912	no	7	1.23144	-1.29923	TIA1	P31483
-1.72294	NaN	-2.80995	no	13	0.824386	-2.26645	TRIM71	Q2Q1W2
-0.64537	-1.60902	-0.81568	no	32	1.12576	-1.02336	TUBA1C	Q9BQE3
-1.45395	-2.04073	NaN	no	8	0.975084	-1.74734	UBE2K	P61086
-1.81909	-1.10315	NaN	no	9	0.81543	-1.46112	UBE2O	Q9C0C9
-1.92676	NaN	-0.93641	no	5	0.673663	-1.43159	UMPS	P11172
-2.14146	NaN	-3.16294	no	9	0.91681	-2.6522	VSNL1	P62760
-1.68859	-0.82074	NaN	no	9	0.673714	-1.25467	YARS2	Q9Y2Z4

Table 6.3 Proteins Identified in 3XFLAG immunoprecipitation

			LFQ Values 3XFLAG OCT4 IP (log2)											
Genename	Uniprot	Pep	WT R1	WT R2	WT R3	lin-min R1	lin-min R2	lin-min R3	lin29-42 R1	lin29-42 R2	lin29-42 R3	lin95-117 R1	lin95-117 R2	lin95-117 R3
AAMP	Q13685	3	22.78	NAN	23.55	24.70	24.28	24.84	NAN	NAN	NAN	NAN	NAN	NAN
AAR2	Q9Y312	4	23.70	NAN	23.72	23.47	23.76	23.71	NAN	NAN	NAN	NAN	NAN	NAN
AATF	Q9NY61	6	NAN	NAN	NAN	NAN	NAN	NAN	25.88	24.12	25.95	24.97	25.16	24.56
ABCB6	Q9NP58	3	NAN	NAN	NAN	NAN	23.51	23.88	NAN	NAN	NAN	NAN	NAN	NAN
ABCB7	O75027	6	25.00	25.88	23.39	23.58	NAN	23.36	NAN	NAN	NAN	NAN	NAN	NAN
ABCC1	P33527	16	26.10	26.52	25.89	26.17	25.70	26.12	NAN	23.25	23.29	24.97	23.39	24.56
ABCE1	P61221	31	25.16	28.05	25.95	27.49	28.00	27.73	28.30	29.15	28.96	27.90	28.17	28.71
ABCF2	Q9UG63	33	26.62	27.17	26.80	26.44	26.23	26.46	29.12	28.50	28.85	27.99	28.55	27.87
ACAA2	P42765	8	23.24	NAN	24.18	NAN	NAN	NAN	NAN	NAN	NAN	23.08	22.83	NAN
ACACA	Q13085	31	25.50	27.80	24.44	26.29	26.62	26.83	24.10	24.59	23.86	25.81	24.66	24.98
ACAD11	Q709F0	7	NAN	NAN	NAN	NAN	NAN	NAN	24.79	24.54	25.37	24.14	24.54	24.09
ACAD9	Q9H845	9	24.89	25.31	24.80	25.38	25.19	25.03	23.91	23.75	24.65	23.94	24.44	24.32
ACADM	P11310	2	NAN	NAN	NAN	NAN	22.76	22.52	NAN	NAN	NAN	NAN	NAN	NAN
ACAP2	Q15057	22	26.57	27.35	25.77	27.34	27.90	28.15	22.59	25.11	23.54	24.76	24.05	25.19
ACAT1	P24752	7	NAN	26.21	NAN	NAN	24.84	24.17	NAN	23.80	23.57	23.93	23.64	24.72
ACBD3	Q9H3P7	8	23.49	23.76	23.78	24.87	24.86	25.19	NAN	23.34	22.86	NAN	NAN	NAN
ACIN1	Q9UKV3	2	NAN	NAN	NAN	NAN	NAN	NAN	24.07	NAN	23.53	NAN	NAN	NAN
ACO2	Q99798	6	NAN	22.72	NAN	NAN	23.33	23.19	NAN	NAN	NAN	NAN	NAN	NAN
ACOT7	O00154	7	24.68	24.96	24.57	24.95	25.19	25.30	23.17	23.51	23.11	24.02	23.57	24.40
ACOX1	Q15067	23	28.42	27.52	28.74	26.76	26.01	26.44	24.61	23.31	23.85	23.37	25.59	25.44
ACP1	P24666	2	NAN	22.47	NAN	NAN	22.88	NAN	NAN	NAN	NAN	NAN	NAN	NAN
ACSL1	P33121	6	NAN	NAN	NAN	NAN	23.36	23.37	NAN	NAN	NAN	NAN	NAN	NAN
ACSL3	O95573	21	25.94	26.29	26.10	26.78	26.79	26.87	25.63	25.66	25.52	26.20	25.84	26.06
ACTG1	P63261	25	NAN	NAN	NAN	NAN	NAN	NAN	26.49	NAN	25.39	NAN	NAN	NAN
ADAM10	O14672	5	22.11	22.76	21.63	23.79	23.25	23.65	21.97	22.19	NAN	NAN	NAN	NAN
ADPGK	Q9BRR6	6	25.06	24.61	24.78	25.03	24.81	25.16	NAN	NAN	NAN	24.06	23.96	24.11
ADSL	P30566	5	NAN	NAN	NAN	NAN	23.67	24.32	NAN	NAN	NAN	NAN	NAN	NAN
AFAP1	Q8N556	20	NAN	24.54	NAN	NAN	23.97	24.26	26.27	25.64	25.72	25.36	25.71	24.80
AFG3L2	Q9Y4W6	11	23.85	24.47	23.90	24.85	25.31	25.34	22.74	NAN	23.18	NAN	NAN	NAN
AGK	Q53H12	10	26.17	25.95	26.84	26.50	26.30	26.55	24.71	24.55	25.01	24.93	25.32	25.25
AGPS	O00116	7	25.02	24.13	24.85	25.01	24.51	24.78	24.02	23.93	NAN	23.61	NAN	24.35
AHCY	P23526	9	23.77	24.77	23.98	25.49	26.33	25.74	NAN	23.56	22.88	23.82	23.51	23.56
AHCYL1	O43865	5	22.93	23.86	23.25	23.65	24.06	23.91	22.97	22.94	23.00	NAN	NAN	NAN
AHSA1	O95433	8	25.32	24.41	25.62	26.33	26.34	26.85	NAN	NAN	NAN	NAN	NAN	NAN
AIFM1	O95831	21	26.10	25.98	26.23	28.28	27.59	28.24	23.78	24.18	23.66	25.13	24.62	24.87
AIMP1	Q12904	7	24.73	25.89	24.50	24.49	24.99	24.99	24.41	25.03	24.40	24.43	24.60	24.74
AKAP1	Q92667	2	NAN	24.46	NAN	NAN	NAN	23.51	NAN	NAN	NAN	NAN	NAN	NAN
AKAP11	Q9UKA4	4	NAN	NAN	NAN	NAN	NAN	NAN	22.09	22.71	NAN	NAN	NAN	NAN
AKAP12	Q02952	4	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	23.36	NAN	23.12
AKAP2	Q9Y2D5	18	24.35	24.78	23.94	23.96	24.98	24.47	26.99	27.32	26.75	26.47	26.23	26.44
AKAP8L	Q9ULX6	6	24.73	23.48	25.35	26.72	24.99	24.77	NAN	NAN	NAN	NAN	NAN	NAN
AKR7A2	O43488	4	NAN	NAN	NAN	NAN	23.86	23.32	NAN	NAN	NAN	NAN	NAN	NAN
AKT1	P31749	6	NAN	24.08	NAN	NAN	24.66	24.41	NAN	NAN	NAN	23.58	22.96	22.99
AKT2	P31751	6	NAN	NAN	NAN	NAN	23.79	23.92	NAN	NAN	NAN	22.68	NAN	23.05
ALCAM	Q13740	14	23.98	25.36	24.03	26.11	26.37	26.65	23.51	24.36	23.27	25.03	24.17	24.94
ALDH18A1	P54886	27	25.66	27.46	25.55	27.30	27.28	26.91	25.58	25.79	25.80	26.05	25.91	26.79
ALDH1A1	P00352	5	23.30	NAN	23.57	23.18	23.56	23.97	NAN	NAN	NAN	NAN	NAN	NAN
ALDH1B1	P30837	16	25.03	26.29	26.25	26.98	26.69	26.73	25.30	24.67	25.50	24.84	25.10	25.45
ALDH5A1	P51649	13	25.56	23.60	25.89	26.66	25.10	25.26	NAN	NAN	NAN	23.65	22.80	NAN
ALDH7A1	P49419	7	NAN	23.86	NAN	NAN	24.50	23.75	NAN	NAN	NAN	24.00	23.67	24.61
ALDH9A1	P49189	9	23.59	23.39	NAN	24.00	24.36	25.25	NAN	NAN	NAN	NAN	NAN	NAN
ALDOC	P09972	5	NAN	NAN	NAN	NAN	25.03	24.46	NAN	NAN	NAN	NAN	NAN	NAN
ALG1	Q9BT22	8	24.35	25.27	24.58	25.11	25.47	25.52	23.17	23.45	NAN	NAN	NAN	NAN
ALG2	Q9H553	7	24.97	26.30	24.44	24.93	24.46	24.52	NAN	NAN	NAN	23.54	23.43	23.54
AMPD2	Q01433	3	NAN	22.54	NAN	NAN	23.00	23.44	NAN	NAN	NAN	NAN	NAN	NAN
ANAPC7	Q9UJX3	2	NAN	NAN	NAN	NAN	22.29	22.10	21.45	NAN	21.71	NAN	NAN	NAN
ANGEL2	Q5VTE6	3	NAN	NAN	NAN	NAN	NAN	NAN	24.01	23.91	23.58	NAN	NAN	NAN
ANKLE2	Q86XL3	5	NAN	23.33	NAN	NAN	23.83	23.98	NAN	NAN	NAN	NAN	NAN	NAN
ANP32E	Q9BTT0	4	24.14	23.45	23.73	24.96	25.85	25.28	NAN	NAN	NAN	24.71	24.16	24.64
ANTXR1	Q9H6X2	7	NAN	NAN	NAN	NAN	NAN	NAN	26.01	23.91	25.49	NAN	NAN	NAN
ANTXR2	P58335	8	NAN	23.29	NAN	NAN	23.03	22.37	24.00	23.13	24.64	23.31	23.99	23.47
ANXA4	P09525	11	23.91	24.59	25.75	25.48	25.33	25.06	24.03	25.35	26.08	25.28	25.65	26.94
ANXA4	P09525	68	30.43	29.78	30.61	32.37	32.18	32.06	29.86	30.69	30.55	30.88	31.07	31.50
ANXA6	P08133	67	NAN	NAN	NAN	NAN	23.63	23.31	NAN	NAN	NAN	NAN	NAN	NAN
ANXA6	P08133	30	NAN	24.72	NAN	NAN	24.99	24.63	24.27	24.61	24.70	NAN	NAN	NAN
AP1G1	O43747	11	23.37	24.93	23.20	24.75	24.71	25.14	22.28	23.30	23.53	24.38	23.55	24.18
AP1M1	Q9BXS5	4	22.11	NAN	NAN	22.80	22.89	22.83	NAN	NAN	NAN	22.89	NAN	22.67
AP2A1	O95782	50	27.78	27.62	28.00	27.94	28.23	28.09	29.95	29.79	30.09	29.23	29.45	29.12
AP2A2	O94973	34	25.63	26.62	25.63	25.87	26.11	25.93	28.15	28.07	28.13	26.79	27.87	27.50
AP2B1	P63010	62	28.17	28.30	28.07	28.48	28.70	28.61	30.12	29.81	30.15	29.37	29.63	29.53
AP2M1	Q96CW1	23	25.88	25.71	26.01	26.28	26.44	26.30	28.22	27.84	27.90	27.45	27.63	27.32
AP3M1	Q9Y2T2	10	24.96	24.40	24.85	25.42	25.44	25.60	24.80	25.20	24.46	24.33	24.63	25.03
AP3S1	Q92572	5	22.07	22.45	22.46	23.61	23.97	24.35	22.32	23.05	22.40	22.19	22.88	22.89
AP4E1	Q9UPM8	4	24.12	NAN	NAN	24.13	23.95	24.17	NAN	NAN	NAN	NAN	NAN	NAN
AP4M1	O00189	5	NAN	NAN	23.76	23.84	24.46	24.19	NAN	NAN	NAN	NAN	NAN	NAN
APEX1	P27695	10	NAN	26.08	NAN	NAN	25.71	25.55	25.26	26.32	25.99	25.75	25.98	26.96
API5	Q9BZZ5	8	NAN	23.35	NAN	NAN	25.02	25.04	25.17	24.95	24.82	23.40	24.29	23.69
APOBEC3C	Q9NRW3	6	NAN	24.14	NAN	NAN	23.24	NAN	27.09	26.63	26.66	25.55	26.49	25.64
APOL2	Q9BQE5	8	23.61	25.01	24.08	24.62	24.57	24.73	23.38	22.96	23.52	23.30	23.06	NAN

APOOL	Q6UXV4	5	23.01	23.00	24.74	23.26	23.17	23.19	22.74	22.51	NAN	23.05	NAN	23.04
APRT	P07741	5	24.22	26.54	24.47	24.37	24.26	24.12	22.34	NAN	24.37	NAN	NAN	NAN
AQR	O60306	4	NAN	24.24	NAN	NAN	23.01	23.14	NAN	NAN	NAN	NAN	NAN	NAN
ARF1	P84077	10	26.50	27.68	NAN	24.99	25.28	25.12	NAN	NAN	NAN	NAN	NAN	NAN
ARF4	P18085	12	27.61	29.35	27.64	26.99	27.07	27.05	26.21	26.56	26.29	26.49	27.04	27.20
ARFGEF2	Q9Y6D5	3	NAN	NAN	NAN	NAN	22.79	22.63	NAN	NAN	NAN	NAN	NAN	NAN
ARHG	P84095	7	23.45	24.97	23.64	24.95	24.39	25.02	NAN	NAN	NAN	NAN	NAN	NAN
ARHGAP1	Q07960	7	24.28	24.64	NAN	23.83	24.44	23.55	NAN	NAN	NAN	23.09	NAN	24.96
ARHGAP22	Q7Z5H3	3	NAN	NAN	NAN	NAN	24.15	23.89	NAN	NAN	NAN	NAN	NAN	NAN
ARHGAP35	Q9NRY4	3	NAN	NAN	NAN	NAN	22.20	22.01	NAN	NAN	NAN	NAN	NAN	NAN
ARHGAP42	A6NI28	13	24.89	25.33	25.54	25.93	25.85	25.98	23.30	23.85	NAN	24.13	NAN	23.83
ARHGDIA	P52565	7	24.71	25.01	25.16	25.77	25.84	25.48	23.81	24.64	24.89	24.97	24.62	25.94
ARHGEF1	Q92888	9	NAN	25.56	NAN	NAN	24.18	23.74	NAN	NAN	NAN	NAN	NAN	NAN
ARIH1	Q9Y4X5	5	NAN	22.65	NAN	NAN	23.34	24.11	NAN	NAN	NAN	NAN	NAN	NAN
ARL6IP5	O75915	3	24.32	25.46	NAN	25.52	25.45	25.00	24.02	23.79	24.67	24.08	24.62	24.43
ARL8B	Q9NVJ2	8	25.12	27.70	26.33	24.64	24.61	24.53	NAN	NAN	NAN	23.36	23.27	NAN
ARMCX3	Q9UH62	7	NAN	23.04	NAN	NAN	24.07	24.09	NAN	NAN	NAN	NAN	NAN	NAN
ARPC1A	Q92747	12	23.99	24.61	24.30	24.05	24.25	23.88	25.21	24.49	24.88	24.67	24.82	24.56
ARPC4	P59998	10	25.36	26.52	25.48	26.94	27.22	26.96	26.63	27.02	26.86	27.35	27.46	27.37
ARPC5	O15511	3	22.10	23.34	22.51	24.01	24.27	23.85	23.61	24.14	23.97	NAN	23.70	24.06
ARPC5L	Q9BPX5	3	NAN	25.14	NAN	NAN	23.71	24.05	24.22	23.96	25.14	NAN	NAN	NAN
ASAH1	Q13510	3	24.05	NAN	24.09	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
ASCC1	Q8N9N2	6	NAN	23.04	NAN	NAN	23.54	NAN	24.26	23.82	23.99	23.81	24.19	23.37
ASCC2	Q9H1I8	13	24.23	24.86	25.01	23.12	23.02	24.00	25.47	24.83	25.52	24.22	25.31	24.39
ASCC3	Q8N3C0	56	26.07	27.02	21.64	26.02	26.60	26.65	28.92	28.13	28.86	27.55	27.81	27.15
ASMTL	O95671	8	NAN	NAN	NAN	NAN	NAN	NAN	24.33	NAN	24.59	NAN	NAN	NAN
ASNA1	O43681	9	24.37	25.08	24.23	25.48	25.56	25.59	NAN	NAN	NAN	NAN	NAN	NAN
ASS	P00966	6	23.96	25.66	NAN	24.13	25.07	25.23	NAN	NAN	NAN	23.43	NAN	24.06
ATAD1	Q8NBU5	9	24.28	26.24	23.77	24.11	23.74	23.78	23.75	23.66	24.92	23.99	23.85	23.90
ATAD3A	Q9NVI7	31	27.49	28.38	27.40	27.67	27.60	27.62	28.45	27.57	27.87	27.83	27.63	27.38
ATAD3B	Q5T9A4	21	25.55	27.27	23.26	NAN	23.32	24.31	24.83	NAN	23.73	23.46	23.86	24.42
ATG3	Q9NT62	6	23.72	NAN	23.41	24.91	24.95	24.74	NAN	NAN	NAN	23.17	NAN	23.35
ATIC	P31939	10	23.14	25.50	NAN	24.06	24.46	23.92	23.54	24.39	NAN	NAN	NAN	NAN
ATL3	Q6DD88	24	27.69	29.13	27.59	28.32	28.18	28.22	26.85	27.00	26.79	27.05	27.22	27.47
ATP13A1	Q9HD20	15	24.66	25.66	23.71	25.51	25.23	25.25	24.04	24.26	23.82	25.12	24.66	24.60
ATP1A1	P05023	38	29.17	28.91	29.00	29.55	29.12	29.39	26.58	26.85	26.60	27.79	27.20	27.80
ATP1B3	P54709	8	25.30	26.56	25.87	26.67	26.49	26.49	23.65	24.33	23.29	24.75	24.44	24.91
ATP2C1	P98194	9	24.41	23.85	24.02	23.92	23.87	24.42	23.22	23.21	22.69	23.68	23.04	23.80
ATP5H	O75947	9	30.49	30.56	31.25	31.17	30.74	30.68	29.60	29.72	29.19	28.59	28.69	29.13
ATP5I	P56385	2	23.53	NAN	23.86	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
ATP5L	O75964	4	24.38	25.29	25.04	26.04	25.89	25.57	22.69	24.01	23.13	24.04	23.53	23.30
ATP6V0A1	Q93050	13	22.91	26.01	NAN	22.55	22.82	NAN	25.89	26.04	24.70	25.85	25.20	26.99
ATP6V0A2	Q9Y487	6	NAN	NAN	NAN	NAN	NAN	NAN	23.54	23.54	23.26	23.61	23.33	23.17
ATP6V0C	P27449	2	NAN	24.58	NAN	NAN	22.59	22.06	23.14	24.29	22.66	NAN	NAN	NAN
ATP6V0D1	P61421	12	22.75	25.70	24.44	24.15	23.92	24.21	26.66	26.66	26.39	27.48	27.50	27.95
ATP6V1C1	P21283	8	NAN	25.13	NAN	NAN	24.89	24.88	NAN	NAN	NAN	NAN	NAN	NAN
ATP6V1E1	P36543	5	24.20	24.48	24.78	23.79	24.49	24.31	24.67	25.13	25.30	24.58	24.93	NAN
ATP6V1G1	O75348	4	NAN	NAN	NAN	NAN	23.39	23.67	NAN	NAN	NAN	NAN	NAN	NAN
ATP6V1H	Q9UI12	10	24.17	25.08	24.54	24.47	24.79	24.80	NAN	NAN	NAN	NAN	NAN	NAN
ATXN10	Q9UBB4	15	24.10	25.86	24.35	25.14	25.40	25.50	24.53	23.80	23.60	23.26	NAN	23.96
ATXN2	Q99700	5	NAN	NAN	NAN	NAN	NAN	NAN	23.85	23.12	23.01	23.22	23.73	23.23
ATXN2L	Q8WWM7	8	23.39	22.55	23.78	NAN	NAN	22.72	22.96	22.95	23.18	23.77	24.17	23.50
AUP1	Q9Y679	6	NAN	24.57	23.65	25.10	24.35	24.99	23.26	23.63	NAN	24.39	25.37	24.47
BAG3	O95817	6	23.90	23.74	23.90	24.29	24.21	23.88	NAN	NAN	NAN	NAN	23.53	23.51
BAG5	Q9UL15	8	25.36	26.59	25.49	25.27	25.04	25.62	24.19	23.55	24.56	23.57	23.19	23.94
BASP1	P80723	5	NAN	NAN	NAN	NAN	NAN	NAN	22.61	23.20	NAN	NAN	NAN	NAN
BAT3	P46379	11	25.26	26.46	25.45	25.64	25.19	25.83	NAN	NAN	NAN	NAN	NAN	NAN
BAX	Q07812	6	24.31	23.87	24.19	23.94	24.05	24.12	NAN	NAN	NAN	NAN	NAN	NAN
BCCIP	Q9P287	4	24.48	25.99	25.40	26.01	26.22	26.08	NAN	NAN	NAN	24.44	25.16	26.46
BCS1L	Q9Y276	3	NAN	NAN	NAN	NAN	22.54	22.89	NAN	NAN	NAN	NAN	NAN	NAN
BGN	P21810	6	NAN	25.37	NAN	NAN	23.61	NAN	26.29	23.12	24.56	24.40	25.14	24.37
BICD2	Q8TD16	19	25.17	24.42	24.89	26.95	26.56	25.98	NAN	NAN	NAN	22.25	22.89	22.93
BLVRA	P53004	3	NAN	NAN	NAN	NAN	22.13	22.35	NAN	NAN	NAN	NAN	NAN	NAN
BOLA2	Q9H3K6	4	24.80	25.57	25.07	25.90	26.02	26.21	NAN	NAN	NAN	NAN	NAN	NAN
BOP1	Q14137	9	24.20	24.22	NAN	23.11	23.53	23.87	25.95	25.33	25.56	25.02	25.05	25.00
BRAT1	Q6PJG6	8	NAN	24.87	NAN	NAN	23.47	23.16	NAN	NAN	NAN	NAN	NAN	NAN
BRIX1	Q8TDN6	18	NAN	24.22	22.52	23.21	24.61	24.07	29.75	29.33	29.43	28.15	29.74	28.17
BSG	P35613	11	26.84	27.08	27.09	28.91	28.24	28.45	25.63	25.80	25.26	26.71	25.64	25.90
BST1	Q10588	9	NAN	NAN	NAN	NAN	NAN	NAN	26.16	25.86	25.68	26.08	26.25	26.17
BTAF1	O14981	3	NAN	23.85	NAN	NAN	22.23	21.91	NAN	NAN	NAN	NAN	NAN	NAN
BTF3L4	Q96K17	4	NAN	NAN	NAN	NAN	NAN	NAN	NAN	26.87	26.49	NAN	26.39	26.80
BUB3	O43684	9	23.25	24.86	24.07	25.77	25.66	25.42	25.34	25.28	25.09	25.72	25.66	25.54
BYSL	Q13895	13	23.40	24.02	23.59	24.14	24.71	24.67	26.31	25.76	25.72	25.43	26.36	25.85
BZW1	Q7L1Q6	11	23.75	26.19	23.87	24.33	25.61	25.40	23.54	24.07	24.24	23.93	24.05	24.52
BZW2	Q9Y6E2	6	23.33	24.65	NAN	23.43	23.58	23.62	NAN	NAN	NAN	NAN	NAN	NAN
C11orf84	Q9BUA3	8	21.68	22.72	24.79	26.13	26.46	25.66	22.49	23.55	22.89	24.03	22.51	22.17
C14orf166	Q9Y224	19	26.14	27.24	27.03	27.18	26.98	26.90	28.74	28.71	29.04	27.95	28.46	27.98
C19orf70	Q5XKP0	4	24.63	25.19	25.37	24.43	23.49	23.67	NAN	NAN	NAN	NAN	NAN	NAN
C1QBP	Q07021	10	28.63	29.82	27.26	28.77	28.35	28.55	26.85	26.60	28.39	25.68	26.22	26.48
C2orf47	Q8WWC4	3	NAN	23.58	NAN	NAN	24.11	24.08	NAN	NAN	NAN	NAN	NAN	NAN
C3orf17	Q6NW34	7	NAN	NAN	NAN	NAN	NAN	NAN	23.83	22.42	23.90	22.24	22.69	21.78
C6orf120	Q7Z4R8	2	NAN	NAN	NAN	NAN	NAN	NAN	24.49	22.88	23.91	NAN	NAN	NAN
C7orf50	Q9BRJ6	9	NAN	NAN	NAN	NAN	NAN	NAN	27.15	26.70	27.22	26.75	27.04	26.26
C8orf33	Q9H7E9	4	NAN	NAN	NAN	NAN	NAN	NAN	24.52	24.28	24.24	22.96	24.04	23.31
C9orf114	Q5T280	6	NAN	NAN	NAN	NAN	NAN	NAN	25.23	24.24	24.80	24.88	24.80	24.69

CACNA2D1	P54289	13	NAN	NAN	NAN	NAN	NAN	NAN	25.69	25.37	25.14	25.86	25.66	26.23
CACYBP	Q9HB71	7	NAN	24.43	23.75	25.17	25.83	25.79	NAN	23.45	23.88	NAN	NAN	NAN
CAD	O76075	63	28.49	28.48	27.17	28.63	28.61	28.74	27.46	27.34	26.59	27.03	26.94	26.84
CALD1	Q05682	59	30.06	29.46	29.71	28.60	28.80	28.68	30.91	30.60	30.55	31.00	31.23	30.87
CALR	P27797	21	29.90	29.31	29.98	31.55	31.29	31.23	28.28	29.03	28.93	29.93	29.78	30.44
CALU	O43852	30	29.54	30.77	29.91	31.12	30.53	30.60	27.60	28.18	27.88	28.80	29.06	29.40
CALU	O43852	26	NAN	NAN	23.25	25.27	24.44	24.70	NAN	NAN	NAN	NAN	NAN	NAN
CAMK2G	Q13555	8	NAN	NAN	NAN	NAN	22.90	23.04	NAN	23.09	22.95	23.38	23.34	23.56
CANX	P27824	39	31.69	30.65	31.81	31.13	31.00	31.02	28.56	29.18	28.82	29.78	29.32	29.73
CAP2	P40123	5	NAN	NAN	NAN	NAN	22.73	22.44	NAN	NAN	NAN	NAN	NAN	NAN
CAPN2	P17655	28	27.42	27.53	27.79	28.51	28.46	28.66	26.44	26.93	26.62	27.47	27.18	27.52
CAPN5	O15484	5	NAN	NAN	NAN	NAN	24.32	24.28	NAN	23.14	23.39	NAN	NAN	NAN
CAV1	Q03135	11	NAN	NAN	NAN	NAN	NAN	NAN	26.57	27.03	26.93	26.89	26.60	27.24
CAV2	P51636	4	23.46	24.98	23.36	23.54	23.02	22.46	27.00	25.41	25.82	25.87	25.91	25.74
CBLL1	Q75N03	2	NAN	NAN	NAN	NAN	23.23	23.25	NAN	NAN	NAN	NAN	NAN	NAN
CBR1	P16152	15	27.34	27.11	27.85	26.97	27.37	27.56	24.90	26.70	25.79	25.17	23.50	26.69
CBX3	Q13185	5	22.41	23.66	23.10	24.96	24.63	24.37	23.32	23.01	23.45	23.39	23.20	23.91
CCT3	P49368	8	24.69	23.84	25.15	24.73	24.95	24.89	NAN	24.67	24.26	NAN	NAN	NAN
CCT4	P50991	42	29.69	29.77	29.99	30.16	30.41	30.39	28.03	29.05	28.15	29.04	28.45	28.94
CCT7	Q99832	35	29.70	29.83	30.00	30.22	30.28	30.25	27.96	28.85	28.13	28.97	28.44	29.03
CCT8	P50990	47	29.49	29.64	29.89	30.13	30.36	30.42	27.76	28.59	27.80	28.99	28.08	28.75
CD151	P48509	3	22.86	22.97	23.63	24.56	24.62	24.29	NAN	NAN	NAN	23.27	NAN	23.75
CD276	Q5ZPR3	5	23.33	24.48	23.39	24.83	24.66	24.68	NAN	NAN	NAN	NAN	NAN	NAN
CD55	P08174	7	NAN	24.01	NAN	NAN	23.38	NAN	24.28	24.46	24.34	24.32	24.47	24.98
CD63	P08962	2	NAN	NAN	NAN	NAN	23.34	22.83	NAN	22.37	22.40	NAN	NAN	NAN
CD81	P60033	5	NAN	26.52	NAN	NAN	26.11	26.08	NAN	NAN	NAN	25.55	NAN	26.18
CD97	P48960	10	24.81	25.50	24.99	25.51	25.13	25.28	NAN	24.19	24.12	24.37	23.83	24.41
CD99	P14209	2	NAN	22.06	NAN	NAN	22.27	22.44	NAN	NAN	NAN	NAN	NAN	NAN
CDC2	P06493	5	23.54	23.77	22.96	NAN	NAN	23.12	23.71	NAN	24.48	NAN	NAN	NAN
CDC27	P30260	5	NAN	NAN	NAN	NAN	NAN	NAN	24.50	NAN	23.99	NAN	NAN	NAN
CDC2L2	Q9UQ88	6	NAN	22.85	NAN	NAN	NAN	23.56	23.91	23.68	24.02	23.87	23.43	22.36
CDC37	Q16543	13	24.60	25.59	24.80	27.19	27.40	27.63	24.19	25.45	25.16	25.44	25.79	25.63
CDC5L	Q99459	8	NAN	24.91	24.58	24.62	24.58	24.20	25.33	24.55	24.84	24.62	25.39	24.39
CDC73	Q6P1J9	9	25.38	23.26	24.65	24.66	24.14	24.63	23.97	24.06	24.83	24.27	23.41	24.13
CDH13	P55290	6	NAN	24.59	NAN	NAN	24.02	23.98	26.79	26.09	26.23	26.81	26.99	27.12
CDIPT	O14735	6	27.64	26.81	27.59	26.38	26.01	26.47	25.25	24.73	25.64	24.69	25.27	24.67
CDK4	P11802	5	NAN	NAN	NAN	NAN	22.59	23.54	21.95	NAN	22.07	NAN	NAN	NAN
CDK5	Q00535	4	NAN	22.82	NAN	NAN	NAN	22.23	NAN	NAN	NAN	23.01	NAN	23.59
CDK5RAP3	Q96JB5	19	22.91	24.71	NAN	25.05	24.72	25.03	25.00	26.69	25.65	26.30	25.25	26.86
CDK9	P50750	5	NAN	NAN	NAN	NAN	NAN	NAN	22.44	21.44	NAN	NAN	NAN	NAN
CDS2	O75420	2	24.19	23.88	24.93	24.40	24.21	24.32	NAN	NAN	NAN	NAN	NAN	NAN
CEBPZ	Q03701	32	NAN	24.29	NAN	NAN	22.47	NAN	28.87	27.77	28.40	27.55	27.91	26.75
CES2	O00748	7	NAN	NAN	NAN	NAN	24.90	24.64	NAN	NAN	NAN	NAN	NAN	NAN
CHCHD3	Q9NX63	13	23.58	NAN	23.62	NAN	NAN	NAN	25.06	25.07	25.03	25.72	25.55	25.58
CHD4	Q14839	23	26.04	26.36	23.42	27.24	26.74	26.39	24.78	24.47	24.42	25.32	24.17	24.38
CHERP	Q8IWX8	5	NAN	23.56	NAN	NAN	23.62	23.41	24.02	NAN	23.39	NAN	NAN	NAN
CHID1	Q9BWS9	5	NAN	23.37	NAN	NAN	22.38	NAN	NAN	NAN	NAN	NAN	NAN	NAN
CHORDC1	Q9UHD1	2	NAN	23.33	NAN	NAN	23.22	23.14	NAN	NAN	NAN	NAN	NAN	NAN
CHP	Q99653	3	NAN	NAN	24.15	24.22	23.84	23.76	NAN	NAN	NAN	NAN	NAN	NAN
CHPF	Q8IZ52	4	23.49	NAN	23.20	22.98	22.70	23.18	NAN	NAN	NAN	NAN	NAN	NAN
CHRNA3	P32297	25	25.46	23.96	25.80	26.91	26.45	26.54	23.69	23.11	22.77	23.41	NAN	23.98
CHST14	Q8NCH0	3	NAN	NAN	NAN	NAN	22.51	22.33	NAN	NAN	NAN	NAN	NAN	NAN
CIAO1	O76071	5	22.87	24.50	23.91	24.02	24.60	24.38	23.21	23.28	22.89	NAN	23.52	23.88
CISD1	Q9NZ45	3	NAN	23.04	NAN	NAN	NAN	23.57	NAN	NAN	NAN	NAN	NAN	NAN
CKAP5	Q14008	32	26.32	26.96	26.61	26.84	27.19	27.27	25.79	26.41	25.89	26.10	26.23	26.78
CKB	P12277	7	NAN	23.98	NAN	NAN	24.66	24.08	NAN	NAN	NAN	NAN	NAN	NAN
CLINT1	Q14677	6	NAN	NAN	NAN	NAN	NAN	NAN	23.66	22.83	24.13	22.24	22.54	22.71
CLN3	Q13286	2	NAN	NAN	NAN	NAN	23.99	25.32	NAN	NAN	NAN	NAN	NAN	NAN
CLPB	Q9H078	6	NAN	22.57	NAN	NAN	23.68	23.68	NAN	NAN	NAN	NAN	NAN	NAN
CLPTM1	O96005	12	25.93	26.43	26.48	26.03	25.20	25.93	NAN	NAN	NAN	23.81	22.90	24.16
CLPTM1L	Q96KA5	4	24.17	23.94	24.54	24.29	24.18	24.16	23.11	23.33	23.54	NAN	NAN	NAN
CLPX	O76031	10	NAN	24.77	24.14	24.74	24.58	24.88	23.80	23.99	23.88	NAN	NAN	NAN
CLTA	P09496	4	NAN	NAN	NAN	NAN	NAN	NAN	22.95	NAN	23.73	NAN	NAN	NAN
CLUH	O75153	16	23.16	25.51	NAN	25.25	25.44	25.79	NAN	NAN	NAN	NAN	NAN	NAN
CMBL	Q96DG6	14	26.03	22.53	26.75	26.99	27.25	27.28	23.10	24.39	24.31	23.27	22.19	23.39
CMSS1	Q9BQ75	5	NAN	NAN	NAN	NAN	NAN	NAN	25.26	24.07	24.65	23.64	24.14	NAN
CNBP	P62633	8	21.56	24.94	21.64	22.36	22.65	22.50	25.15	24.78	24.73	23.52	25.06	25.24
CNOT1	A5YKK6	26	25.12	25.58	24.09	25.53	25.42	25.76	26.39	26.05	26.37	25.87	26.78	25.74
CNOT7	Q9UIV1	4	21.91	23.29	NAN	22.31	23.20	22.61	23.80	22.94	23.69	23.08	23.74	22.38
CNTNAP1	P78357	18	26.37	26.09	22.93	27.33	27.73	27.86	24.40	23.55	23.06	25.27	24.01	25.16
COMT	P21964	15	28.08	28.90	27.39	27.67	27.43	27.38	26.17	26.78	26.53	26.78	27.08	26.94
COPS5	Q92905	11	24.62	23.62	24.22	25.94	26.27	26.26	22.59	23.30	22.44	23.34	NAN	23.30
COPS6	Q7L5N1	11	25.39	25.22	25.71	26.71	26.73	26.59	NAN	25.93	23.94	24.69	NAN	24.71
COPS7B	Q9H9Q2	2	25.82	NAN	25.82	24.62	24.56	24.78	NAN	NAN	NAN	22.76	22.49	NAN
COPS8	Q99627	6	25.20	23.37	24.02	26.67	26.54	25.95	NAN	23.47	23.86	23.58	NAN	23.61
CORO2B	Q9UQ03	3	NAN	NAN	NAN	NAN	NAN	NAN	NAN	22.84	23.57	NAN	NAN	NAN
COTL1	Q14019	4	NAN	24.71	NAN	NAN	NAN	23.47	NAN	23.60	24.08	NAN	23.63	23.91
COX2	P00403	8	25.99	26.28	26.27	26.67	25.86	25.55	28.18	28.38	28.34	27.10	27.06	27.07
COX4I1	P13073	9	23.78	23.97	24.24	25.46	25.13	25.01	25.64	25.76	25.89	25.35	24.86	24.90
COX5A	P20674	6	NAN	25.64	24.91	24.23	24.18	24.50	25.78	25.73	26.36	24.45	24.32	24.35
COX5B	P10606	2	NAN	22.14	NAN	NAN	22.54	22.67	24.23	24.58	24.85	23.66	24.48	24.39
COX6A1	P12074	2	23.08	NAN	23.64	NAN	NAN	NAN	24.04	25.49	25.05	NAN	NAN	NAN
COX6C	P09669	3	21.78	NAN	22.31	NAN	NAN	NAN	23.61	24.10	23.76	NAN	NAN	NAN
CPD	O75976	6	24.34	24.77	NAN	23.73	23.00	23.30	NAN	NAN	NAN	NAN	NAN	NAN
CPNE1	Q99829	4	24.53	25.17	24.71	23.92	23.37	23.45	23.25	22.67	23.70	23.37	23.08	23.79

CPNE2	Q96FN4	5	NAN	NAN	NAN	NAN	NAN	NAN	23.76	23.81	23.48	23.78	24.20	24.45
CPNE3	O75131	26	27.21	26.80	27.73	27.44	27.26	27.26	28.94	28.45	28.58	28.50	28.80	28.84
CPNE8	Q86YQ8	5	NAN	NAN	NAN	NAN	NAN	NAN	23.20	22.92	22.98	22.75	23.49	23.48
CPSF1	Q10570	9	NAN	NAN	NAN	NAN	23.59	23.96	NAN	NAN	NAN	NAN	NAN	NAN
CPSF2	Q9P2I0	9	NAN	NAN	NAN	NAN	23.07	22.80	NAN	NAN	NAN	NAN	NAN	NAN
CPT1A	P50416	24	27.58	26.22	27.99	27.71	27.50	27.73	25.75	25.76	26.01	26.74	26.48	26.67
CRIP2	P52943	4	NAN	25.64	NAN	NAN	24.40	24.02	23.77	24.04	23.93	NAN	24.85	25.66
CROP	O95232	12	NAN	23.20	NAN	NAN	24.04	NAN	26.10	25.77	26.59	26.07	25.57	25.14
CRTAP	O75718	21	27.04	26.56	27.55	28.85	28.46	28.59	26.23	26.60	26.32	27.35	26.67	27.13
CRYAB	P02511	19	29.78	28.71	30.25	28.06	28.13	28.37	27.00	27.22	26.74	26.79	26.91	27.11
CRYZL1	O95825	2	22.76	NAN	23.41	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
CS	O75390	10	24.44	24.87	24.20	26.42	26.24	25.71	23.94	24.27	24.81	24.62	24.94	25.41
CSDA	P16989	2	NAN	22.34	NAN	NAN	22.34	NAN	22.43	22.09	22.26	22.65	22.19	21.99
CSDE1	O75534	9	NAN	NAN	NAN	NAN	NAN	NAN	23.19	NAN	23.05	NAN	NAN	NAN
CSNK1A1	P48729	41	27.13	28.76	27.43	28.11	28.20	28.33	25.88	27.07	26.96	26.45	25.84	26.69
CSNK1A1	P48729	6	23.67	23.53	NAN	23.47	23.58	23.85	24.72	24.12	24.36	NAN	NAN	NAN
CSNK1E	P49674	2	NAN	21.52	NAN	NAN	22.40	22.79	NAN	NAN	NAN	NAN	NAN	NAN
CSNK2A2	P19784	15	24.79	25.84	24.98	25.49	25.29	25.49	26.55	26.28	26.09	25.44	26.11	25.40
CSTA	P01040	3	23.53	23.37	23.52	23.36	22.46	22.94	NAN	NAN	NAN	NAN	NAN	NAN
CSTB	P04080	3	23.18	24.02	23.34	25.86	25.54	25.94	NAN	23.90	23.24	NAN	22.93	23.23
CSTF1	Q05048	4	24.02	23.64	24.27	24.04	24.37	24.19	24.29	24.52	NAN	NAN	NAN	NAN
CSTF3	Q12996	6	23.12	24.70	NAN	24.02	23.83	23.62	NAN	NAN	NAN	22.67	22.51	23.23
CTBP1	Q13363	13	24.00	24.42	24.70	25.88	25.92	25.62	23.45	24.12	23.27	24.48	24.41	24.88
CTBP2	P56545	11	NAN	24.73	23.50	24.89	24.52	24.99	23.06	24.12	24.01	NAN	NAN	NAN
CTNNBL1	Q8WYA6	7	NAN	NAN	NAN	NAN	24.32	24.12	24.37	23.64	23.79	24.15	23.98	24.06
CTPS1	P17812	17	26.27	26.90	26.62	26.07	26.39	26.19	25.17	25.39	25.00	24.93	25.44	25.57
CTSB	P07858	12	28.17	26.70	28.69	29.34	29.29	29.69	26.86	27.56	27.37	27.96	27.51	27.87
CUL1	Q13616	4	NAN	22.56	NAN	NAN	22.62	22.89	NAN	NAN	NAN	NAN	NAN	NAN
CUL3	Q13618	5	NAN	22.81	NAN	NAN	NAN	23.02	NAN	NAN	NAN	NAN	NAN	NAN
CUL5	Q93034	8	NAN	NAN	23.55	23.26	23.26	23.05	24.28	23.53	24.22	23.52	23.47	NAN
CWC22	Q9HCG8	2	NAN	NAN	NAN	NAN	NAN	NAN	NAN	19.96	20.19	NAN	NAN	NAN
CYB5B	O43169	5	25.16	26.29	25.40	25.89	25.65	25.67	NAN	24.78	24.08	NAN	NAN	NAN
CYB5R1	Q9UHQ9	4	NAN	NAN	NAN	NAN	NAN	NAN	24.99	24.78	NAN	NAN	25.43	25.05
CYB5R3	P00387	20	28.25	30.17	28.56	29.38	29.25	29.17	28.87	29.14	28.98	29.55	29.49	29.99
CYC1	P08574	7	25.86	24.83	26.41	26.21	26.70	26.69	25.39	25.99	25.90	25.98	25.18	26.08
CYCS	P99999	4	NAN	23.23	NAN	NAN	23.34	23.23	NAN	NAN	NAN	NAN	NAN	NAN
CYP51A1	Q16850	8	NAN	26.01	22.20	23.24	23.53	23.27	NAN	NAN	NAN	NAN	NAN	NAN
CYTSA	Q69YQ0	36	23.24	27.30	23.75	22.55	22.26	21.73	28.75	27.70	28.93	26.55	26.38	25.90
DAB2	P98082	6	NAN	NAN	NAN	NAN	NAN	NAN	24.71	24.30	24.22	23.81	24.78	23.89
DAD1	P61803	3	22.81	24.65	23.28	25.68	25.37	24.99	NAN	NAN	NAN	NAN	NAN	NAN
DAZAP1	Q96EP5	4	22.75	22.97	22.86	24.35	23.77	23.43	NAN	NAN	NAN	23.21	23.81	23.70
DBNL	Q9UJU6	6	NAN	NAN	NAN	NAN	NAN	NAN	NAN	23.81	24.39	NAN	NAN	NAN
DBT	P11182	2	22.98	NAN	23.33	22.53	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
DCAF6	Q58WW2	5	NAN	NAN	NAN	NAN	23.52	23.66	NAN	NAN	NAN	NAN	NAN	NAN
DCAF7	P61962	4	23.67	23.15	24.08	24.04	24.28	23.78	NAN	NAN	NAN	NAN	NAN	NAN
DCN	P07585	6	NAN	NAN	NAN	NAN	NAN	NAN	23.35	23.04	23.49	25.41	25.06	24.68
DCPS	Q96C86	3	NAN	NAN	NAN	NAN	22.67	22.22	NAN	NAN	NAN	NAN	NAN	NAN
DDHD1	Q8NEL9	2	NAN	NAN	NAN	NAN	22.31	22.04	NAN	NAN	NAN	NAN	NAN	NAN
DDRGK1	Q96HY6	7	24.16	24.88	24.58	24.99	24.63	24.19	25.36	25.50	25.99	25.48	25.73	26.04
DDX10	Q13206	14	NAN	NAN	NAN	NAN	NAN	NAN	25.15	23.68	24.94	23.18	23.78	23.49
DDX17	Q92841	35	25.41	26.20	25.43	26.77	26.62	26.49	28.56	27.70	27.97	28.06	28.38	27.55
DDX18	Q9NVP1	26	NAN	NAN	NAN	NAN	NAN	NAN	28.83	27.42	28.49	26.78	27.76	26.81
DDX20	Q9UHI6	6	NAN	NAN	NAN	NAN	NAN	NAN	24.57	NAN	24.30	24.01	24.14	NAN
DDX21	Q9NR30	63	26.54	28.67	28.01	27.03	28.07	27.33	32.28	31.61	31.99	31.56	32.11	31.34
DDX24	Q9GZR7	31	23.51	25.73	24.57	21.87	23.97	22.84	29.00	27.01	27.43	27.10	28.10	26.70
DDX27	Q96GQ7	9	NAN	NAN	NAN	NAN	NAN	NAN	25.42	24.64	24.75	25.30	25.80	24.98
DDX31	Q9H8H2	15	NAN	NAN	NAN	NAN	NAN	NAN	26.57	25.75	25.94	25.10	26.00	25.27
DDX39A	O00148	17	25.59	25.15	25.71	24.85	24.94	24.93	23.98	23.95	NAN	NAN	NAN	NAN
DDX39B	Q13838	19	27.09	27.31	27.07	28.10	27.87	28.00	25.58	26.31	25.75	26.49	26.40	26.87
DDX41	Q9UJV9	4	NAN	NAN	NAN	NAN	NAN	NAN	NAN	23.15	24.52	NAN	NAN	NAN
DDX42	Q86XP3	17	NAN	23.39	24.82	27.46	27.27	27.04	25.91	25.62	25.44	26.04	26.28	26.45
DDX46	Q7L014	8	NAN	NAN	NAN	NAN	NAN	NAN	23.93	23.84	24.79	24.75	NAN	23.08
DDX47	Q9H0S4	10	NAN	25.10	22.30	24.47	24.08	23.62	27.08	25.31	26.30	25.30	26.37	24.75
DDX48	P38919	23	25.36	25.36	25.84	26.30	26.20	26.37	25.97	25.59	26.02	25.95	25.57	25.69
DDX49	Q9Y6V7	6	NAN	24.29	23.33	22.68	22.64	22.77	23.36	NAN	23.21	23.02	23.52	NAN
DDX5	P17844	40	27.53	28.75	28.05	28.89	28.68	28.64	30.60	29.58	29.97	29.88	30.24	29.62
DDX50	Q9BQ39	30	NAN	NAN	NAN	NAN	NAN	NAN	28.85	27.72	28.35	28.28	27.86	26.81
DDX51	Q8N8A6	9	NAN	NAN	NAN	NAN	NAN	NAN	25.16	24.37	25.71	24.42	24.69	24.26
DDX52	Q9Y2R4	15	NAN	NAN	NAN	NAN	NAN	NAN	26.74	25.52	26.74	25.15	26.23	24.53
DDX54	Q8TDD1	26	NAN	NAN	NAN	NAN	NAN	NAN	27.43	26.83	27.23	26.40	26.63	25.81
DDX55	Q8NHQ9	10	NAN	NAN	NAN	NAN	NAN	NAN	26.60	25.10	26.66	23.71	23.82	23.00
DDX56	Q9NY93	8	NAN	24.68	NAN	NAN	23.50	NAN	25.25	24.77	25.43	24.75	25.02	24.42
DDX6	P26196	14	24.72	26.22	25.21	26.58	26.75	26.65	27.22	27.17	26.83	26.80	27.55	27.03
DECR1	Q16698	19	21.88	22.63	21.79	24.19	24.25	23.96	29.84	29.55	30.25	28.63	28.84	28.66
DEK	P35659	6	NAN	NAN	NAN	NAN	NAN	NAN	26.34	25.29	25.70	24.91	24.87	24.47
DERL1	Q9BUN8	2	24.41	24.88	24.99	24.79	NAN	24.61	NAN	NAN	NAN	NAN	NAN	NAN
DGKA	P23743	10	NAN	24.42	24.02	24.09	24.48	24.05	24.88	24.68	24.53	24.50	24.80	25.31
DHCR24	Q15392	5	NAN	23.41	23.98	24.39	23.60	24.17	23.02	23.06	23.21	22.92	23.58	23.21
DHCR7	Q9UBM7	3	22.55	NAN	23.16	NAN	22.13	22.22	NAN	NAN	NAN	NAN	NAN	NAN
DHPS	P49366	9	24.61	NAN	24.53	26.18	25.53	26.51	NAN	NAN	NAN	NAN	NAN	NAN
DHRS7	Q9Y394	4	NAN	25.45	NAN	NAN	23.64	23.56	NAN	NAN	NAN	NAN	NAN	NAN
DHX15	O43143	33	27.39	28.32	27.44	27.44	27.67	27.73	28.45	28.06	28.37	28.23	28.31	27.98
DHX29	Q7Z478	43	NAN	25.31	NAN	NAN	22.26	23.81	28.77	27.99	28.87	27.17	27.89	27.10
DHX30	Q7L2E3	52	20.49	25.87	23.45	22.98	24.09	24.40	29.90	29.00	29.40	28.92	29.00	28.42
DHX37	Q8IY37	9	NAN	24.66	NAN	NAN	NAN	22.63	25.68	24.18	25.32	24.21	24.79	23.93

DHX57	Q6P158	25	NAN	23.24	NAN	NAN	22.69	22.49	27.96	26.12	27.97	25.91	26.73	25.26
DHX9	Q08211	58	28.13	29.21	28.03	29.15	29.24	29.12	30.31	29.49	29.76	29.36	29.78	29.17
DIAPH1	O60610	14	26.35	26.16	24.29	25.34	26.23	25.81	NAN	23.40	22.54	NAN	NAN	NAN
DICER1	Q9UPY3	4	NAN	NAN	NAN	NAN	22.11	22.28	NAN	NAN	NAN	NAN	NAN	NAN
DIEXF	Q68CQ4	7	NAN	23.30	NAN	NAN	23.50	23.45	NAN	NAN	NAN	NAN	NAN	NAN
DIMT1	Q9UNQ2	12	NAN	23.72	22.75	21.99	23.56	21.74	27.89	26.95	27.07	26.07	26.75	25.63
DIS3	Q9Y2L1	8	NAN	24.54	22.42	23.46	23.25	23.44	NAN	NAN	NAN	NAN	NAN	NAN
DKC1	O60832	17	24.19	25.35	23.64	22.05	23.26	21.26	29.30	28.15	28.75	28.42	28.68	27.85
DNAJA1	P31689	26	29.78	28.99	29.81	29.68	29.44	29.91	28.13	28.08	28.06	27.42	27.95	27.64
DNAJA2	O60884	20	28.89	28.01	29.34	28.79	28.89	29.21	26.73	26.84	26.89	27.24	26.91	26.71
DNAJA3	Q96EY1	10	26.24	26.11	25.07	27.49	26.98	27.15	25.96	25.48	25.97	25.32	25.22	24.91
DNAJB1	P25685	9	23.45	24.87	23.69	25.70	25.26	25.61	23.40	23.88	NAN	24.51	24.13	23.81
DNAJB11	Q9UBS4	13	27.24	25.85	27.44	28.29	27.77	27.80	25.37	25.36	24.79	25.95	25.11	25.86
DNAJB12	Q9NXW2	5	NAN	NAN	NAN	NAN	23.72	23.84	NAN	NAN	NAN	NAN	NAN	NAN
DNAJB2	P25686	8	NAN	NAN	24.14	24.45	24.18	25.21	NAN	NAN	NAN	23.75	NAN	23.70
DNAJB4	Q9UDY4	7	NAN	NAN	NAN	NAN	23.53	23.51	23.94	23.68	23.46	23.96	23.89	23.71
DNAJB6	O75190	9	23.48	24.06	24.21	25.89	25.82	25.95	23.61	22.41	23.70	NAN	23.61	23.15
DNAJC11	Q9NVH1	14	25.34	26.05	25.63	25.07	24.76	25.03	26.55	25.77	25.94	26.41	25.99	26.22
DNAJC16	Q9Y2G8	3	NAN	24.74	NAN	NAN	22.76	NAN	22.83	22.29	24.31	23.19	23.81	NAN
DNAJC21	Q5F1R6	4	NAN	NAN	NAN	NAN	NAN	NAN	24.13	23.84	23.58	23.63	23.60	23.73
DNAJC3	Q13217	7	25.49	25.52	24.86	24.60	25.16	24.86	NAN	NAN	NAN	24.29	24.27	23.62
DNAJC7	Q99615	34	27.26	25.67	27.34	28.81	28.89	29.05	25.49	26.74	25.41	26.31	25.92	26.28
DNAJC8	O75937	4	NAN	22.10	NAN	NAN	23.81	23.61	NAN	NAN	NAN	NAN	NAN	NAN
DNAJC9	Q8WXX5	3	NAN	NAN	NAN	NAN	NAN	NAN	24.21	23.52	23.85	NAN	NAN	NAN
DNAPTP6	Q9NUQ6	23	NAN	20.46	NAN	NAN	21.76	NAN	28.23	27.87	28.21	26.84	27.14	26.25
DND1	Q8IYX4	2	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	28.12	NAN	27.84
DNM1L	O00429	8	23.68	24.48	NAN	23.88	23.92	23.80	NAN	NAN	NAN	NAN	NAN	NAN
DNM2	P50570	17	NAN	26.60	NAN	NAN	24.79	25.22	24.15	24.03	25.23	23.87	24.94	25.43
DNMT1	P26358	2	NAN	24.60	NAN	NAN	22.23	22.17	NAN	NAN	NAN	NAN	NAN	NAN
DNPEP	Q9ULA0	10	24.33	25.17	24.55	24.35	24.22	24.53	NAN	NAN	NAN	24.08	NAN	24.11
DPCD	Q9BVM2	3	NAN	22.52	NAN	NAN	23.02	23.29	NAN	NAN	NAN	NAN	NAN	NAN
DPP7	Q9UHL4	10	22.71	26.55	22.56	23.83	24.00	24.02	21.82	22.95	23.94	23.75	24.03	23.71
DPY30	Q9C005	2	NAN	NAN	NAN	NAN	NAN	NAN	22.95	NAN	23.66	NAN	NAN	NAN
DPYSL3	Q14195	17	24.81	25.92	25.03	25.86	26.14	26.09	24.93	24.98	25.03	24.47	25.28	25.76
DRG1	Q92597	14	24.75	26.42	NAN	26.43	26.55	26.34	26.43	25.71	26.79	26.48	26.71	26.71
DRG2	P55039	5	NAN	23.46	NAN	NAN	23.34	23.47	NAN	NAN	NAN	NAN	NAN	NAN
DST	Q03001	46	NAN	NAN	NAN	NAN	NAN	NAN	22.57	NAN	22.99	NAN	NAN	NAN
EBNA1BP2	Q99848	14	NAN	22.95	NAN	NAN	21.73	NAN	28.29	27.32	27.84	26.22	26.80	25.78
EBP	Q15125	2	NAN	23.74	NAN	NAN	24.21	24.47	NAN	NAN	NAN	NAN	23.27	23.46
ECD	O95905	5	23.68	24.13	24.04	NAN	23.53	23.57	23.30	23.49	24.55	23.09	24.22	NAN
ECE1	P42892	8	NAN	NAN	NAN	NAN	25.12	24.63	NAN	NAN	NAN	24.24	23.73	24.08
ECHS1	P30084	5	NAN	25.49	24.07	25.29	24.65	24.85	23.23	23.94	24.98	24.04	23.77	24.07
ECM29	Q5VYK3	16	24.81	25.24	NAN	24.73	25.08	25.35	NAN	NAN	NAN	NAN	NAN	NAN
ECM29	Q5VYK3	11	25.41	NAN	23.97	24.07	24.28	24.76	NAN	NAN	NAN	NAN	NAN	NAN
EDC4	Q6P2E9	6	NAN	NAN	NAN	NAN	23.30	22.95	24.90	25.21	25.41	25.25	25.05	24.87
EDEM3	Q9BZQ6	8	24.00	23.83	24.32	26.03	25.50	25.46	NAN	NAN	NAN	23.95	NAN	24.48
EEF1A2	Q05639	18	24.29	25.74	24.56	27.12	27.04	26.96	24.21	NAN	23.30	NAN	NAN	NAN
EEF2	P13639	61	30.65	30.85	31.04	30.79	30.91	31.01	31.18	31.44	31.73	30.48	31.08	31.31
EEFSEC	P57772	5	NAN	NAN	NAN	NAN	NAN	NAN	24.80	24.03	24.45	NAN	NAN	NAN
EFEMP2	O95967	7	NAN	NAN	NAN	NAN	NAN	NAN	23.30	23.62	NAN	23.35	23.32	23.33
EFHD2	Q96C19	11	22.60	27.12	NAN	22.89	22.73	22.67	25.17	23.94	25.35	23.31	24.47	23.63
EGFR	P00533	8	NAN	24.35	NAN	NAN	24.70	24.34	NAN	NAN	NAN	NAN	NAN	NAN
EHD1	Q9H4M9	19	26.04	27.64	25.96	26.06	26.32	26.34	26.03	25.49	26.26	25.14	26.02	26.20
EHD4	Q9H223	12	NAN	24.87	22.46	23.19	23.77	23.53	NAN	NAN	NAN	NAN	NAN	NAN
EIF2A	Q9BY44	10	23.18	25.64	NAN	23.81	24.17	23.68	NAN	23.23	24.51	NAN	24.70	24.05
EIF2AK2	P19525	5	23.56	23.70	23.61	22.94	23.05	23.03	23.41	23.13	23.15	23.24	23.63	23.38
EIF2B1	Q14232	4	NAN	NAN	NAN	NAN	22.19	22.69	NAN	NAN	NAN	NAN	22.90	22.72
EIF2B2	P49770	2	NAN	NAN	NAN	NAN	NAN	NAN	22.91	23.06	23.10	NAN	NAN	NAN
EIF2B3	Q9NR50	6	24.32	24.44	24.89	24.42	25.00	25.25	24.04	24.82	23.71	24.09	24.22	24.13
EIF2B4	Q9UI10	6	24.18	23.98	24.37	24.19	24.33	23.89	24.30	24.03	24.14	24.03	24.28	NAN
EIF2B5	Q13144	6	24.84	24.88	23.96	23.91	22.98	22.96	24.59	23.60	24.13	NAN	NAN	NAN
EIF2C2	Q9UKV8	11	NAN	23.35	24.53	24.26	24.49	24.22	26.22	25.74	25.96	25.80	26.15	25.74
EIF2S1	P05198	20	25.34	26.82	25.51	26.95	26.91	26.78	27.65	27.69	27.75	27.05	27.37	27.91
EIF2S2	P20042	14	24.51	25.94	24.35	25.82	26.11	25.72	24.92	25.59	24.91	25.52	25.30	25.64
EIF2S3	P41091	22	25.82	27.46	26.07	27.74	27.89	27.79	27.53	27.95	27.54	27.89	27.80	28.06
EIF3D	O15371	27	27.95	28.31	28.37	28.14	27.78	27.84	28.64	28.46	28.32	28.22	28.42	28.41
EIF3S1	O75822	11	23.72	24.34	24.46	26.41	26.02	25.99	26.48	25.86	26.10	26.01	26.45	25.91
EIF4A1	P60842	31	28.83	29.46	28.89	29.25	29.41	29.14	29.86	29.65	29.75	29.07	29.74	29.55
EIF4A2	Q14240	22	24.32	24.58	24.82	25.65	25.91	25.26	25.71	25.85	25.96	25.82	25.66	26.21
EIF4B	P23588	20	26.38	27.07	26.23	27.14	27.40	27.42	27.25	27.52	27.65	27.24	27.28	27.20
EIF4E2	O60573	4	NAN	NAN	NAN	NAN	23.85	23.87	NAN	NAN	NAN	24.25	24.58	24.65
EIF4G1	Q04637	55	27.92	28.38	27.71	28.02	27.99	27.93	29.35	29.06	29.10	28.77	29.22	28.93
EIF4G2	P78344	17	24.25	26.04	24.99	24.91	25.48	25.48	25.20	24.60	25.44	24.95	25.60	25.31
EIF4H	Q15056	6	24.40	25.35	25.00	24.86	25.28	25.09	23.70	24.33	25.00	24.12	24.82	25.29
EIF5	P55010	8	NAN	24.39	NAN	NAN	25.98	25.84	25.26	25.04	25.21	24.69	25.27	25.59
EIF5A	P63241	14	26.95	27.83	27.56	27.88	27.89	28.10	26.59	26.90	26.78	26.13	26.34	26.76
EIF6	P56537	12	25.11	25.57	26.44	25.96	26.12	26.28	28.33	28.83	28.91	28.12	28.54	28.17
ELAC2	Q9BQ52	15	23.15	25.45	NAN	26.60	26.47	26.81	25.22	25.49	25.64	24.81	25.64	25.84
ELMO2	Q96JJ3	3	23.32	NAN	23.15	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
ELP2	Q6IA86	12	24.45	24.39	25.17	24.90	25.44	25.55	23.77	23.49	23.60	NAN	NAN	NAN
ELP3	Q9H9T3	11	25.20	24.58	24.81	25.91	26.12	26.35	NAN	NAN	NAN	24.51	24.19	NAN
EMC2	Q15006	9	24.28	24.25	25.00	24.92	25.08	24.78	23.97	23.88	23.87	24.59	24.28	24.63
EMC3	Q9P0I2	4	NAN	NAN	24.23	24.56	24.29	23.87	NAN	NAN	NAN	NAN	NAN	NAN
EMC4	Q5J8M3	2	NAN	23.14	NAN	NAN	24.27	24.15	NAN	NAN	NAN	NAN	NAN	NAN
EMC8	O43402	3	NAN	22.67	NAN	NAN	23.87	23.06	NAN	NAN	NAN	NAN	NAN	NAN

EMG1	Q92979	6	NAN	22.92	NAN	NAN	24.50	24.09	24.05	24.05	24.50	24.14	23.91	24.20
ENAH	Q8N8S7	11	24.23	25.00	23.20	24.09	24.49	24.33	23.87	24.01	23.92	NAN	NAN	NAN
ENDOD1	O94919	15	25.26	NAN	24.42	NAN	NAN	NAN	25.75	25.60	25.85	25.66	25.38	25.98
ENDOG	Q14249	2	NAN	NAN	NAN	NAN	22.23	22.31	NAN	NAN	NAN	NAN	NAN	NAN
ENO1	P06733	29	28.39	29.19	28.71	29.73	30.09	29.82	26.96	28.65	28.73	28.76	28.99	29.48
EPB41L3	Q9Y2J2	4	NAN	NAN	NAN	NAN	23.50	23.19	NAN	NAN	NAN	NAN	NAN	NAN
EPB41L5	Q9HCM4	2	NAN	NAN	NAN	NAN	NAN	NAN	NAN	21.62	21.84	21.69	22.22	NAN
EPHA2	P29317	8	24.16	24.73	NAN	24.83	24.48	24.64	NAN	NAN	NAN	NAN	NAN	NAN
EPHX1	P07099	13	NAN	25.36	24.89	25.16	25.37	24.85	24.54	25.16	24.36	24.90	24.89	24.89
EPN1	Q9Y6I3	4	NAN	NAN	NAN	NAN	NAN	NAN	24.46	25.95	25.51	23.36	24.95	26.07
EPPK1	P58107	15	NAN	NAN	NAN	NAN	NAN	NAN	23.93	NAN	24.53	NAN	NAN	NAN
EPS15	P42566	8	NAN	NAN	NAN	NAN	22.62	22.65	NAN	22.89	22.21	22.79	23.04	23.37
EPS15L1	Q9UBC2	3	NAN	NAN	NAN	NAN	22.64	22.12	NAN	NAN	NAN	NAN	NAN	NAN
ERGIC1	Q969X5	10	27.13	25.96	27.71	27.41	27.25	27.21	24.65	25.32	24.73	26.09	25.46	26.13
ERLIN2	O94905	21	24.17	26.39	24.36	22.61	22.39	23.28	28.86	26.96	28.40	27.13	27.78	27.27
ERO1L	Q96HE7	9	25.28	24.82	25.46	25.43	25.72	25.31	NAN	24.60	23.99	25.00	25.09	25.64
ERP29	P30040	8	23.47	24.67	24.21	24.96	25.01	24.26	23.58	24.41	24.36	24.06	24.44	25.28
ERP44	Q9BS26	11	25.90	24.95	25.70	26.46	26.75	26.90	24.40	25.40	25.13	26.07	25.72	26.90
ERP70	P13667	39	27.48	26.49	27.59	29.15	28.71	28.62	25.02	26.35	26.00	27.45	27.10	27.86
ETF1	P62495	30	28.70	26.44	28.89	30.61	30.46	30.65	27.80	28.14	28.10	28.52	28.37	28.28
ETFA	P13804	9	25.18	26.35	25.05	25.89	25.59	25.42	24.60	23.80	25.41	24.61	24.54	25.28
ETFB	P38117	8	NAN	23.39	23.51	24.51	24.03	24.22	22.81	23.37	23.63	23.89	23.07	23.31
EWSR1	Q01844	6	24.28	24.78	NAN	26.39	26.05	26.24	NAN	24.67	24.18	23.63	24.00	23.91
EXOC1	Q9NV70	7	NAN	NAN	NAN	NAN	NAN	NAN	22.93	23.55	23.59	NAN	22.72	22.78
EXOC3	O60645	3	22.46	NAN	22.78	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
EXOC3L4	Q17RC7	2	NAN	NAN	NAN	NAN	23.55	23.64	NAN	NAN	NAN	24.47	24.54	24.29
EXOC4	Q96A65	8	NAN	24.54	NAN	NAN	23.33	NAN	24.45	23.88	24.02	23.27	NAN	23.62
EXOC6B	Q9Y2D4	3	22.20	24.71	21.60	NAN	21.63	21.49	NAN	NAN	NAN	NAN	NAN	NAN
EXOG	Q9Y2C4	2	NAN	NAN	NAN	NAN	22.58	22.69	NAN	NAN	NAN	NAN	NAN	NAN
EXOSC10	Q01780	11	NAN	23.71	23.54	24.64	24.31	24.03	24.37	24.10	24.23	24.67	25.19	23.85
EXOSC2	Q13868	4	NAN	NAN	NAN	NAN	23.86	24.26	23.84	23.81	24.43	23.87	24.33	23.83
EXOSC3	Q9NQT5	4	NAN	NAN	NAN	NAN	24.20	24.04	24.81	24.00	23.80	24.48	24.69	24.26
EXOSC4	Q9NPD3	4	23.03	NAN	23.60	23.77	23.37	23.47	24.20	23.89	24.27	24.05	24.11	24.10
EXOSC5	Q9NQT4	3	NAN	NAN	NAN	NAN	23.87	23.69	NAN	NAN	NAN	NAN	NAN	NAN
EXOSC6	Q5RKV6	6	NAN	NAN	NAN	NAN	23.82	23.66	24.35	24.40	23.91	24.34	24.25	24.11
EXOSC7	Q15024	4	NAN	24.39	NAN	NAN	NAN	23.47	NAN	NAN	NAN	NAN	NAN	NAN
EXOSC7	Q15024	4	NAN	NAN	NAN	NAN	24.58	24.12	24.13	24.24	24.35	NAN	NAN	NAN
EXOSC8	Q96B26	3	NAN	NAN	NAN	NAN	22.10	21.98	22.49	NAN	22.62	22.08	23.43	NAN
EXOSC9	Q06265	4	NAN	23.98	24.81	24.85	24.43	24.58	24.85	24.30	24.24	23.80	24.64	NAN
FACL4	O60488	11	23.74	26.53	22.86	25.16	25.30	24.55	24.42	24.26	23.03	23.30	24.58	24.23
FAM114A1	Q8IWE2	3	22.83	NAN	NAN	23.30	23.85	23.42	NAN	NAN	NAN	NAN	NAN	NAN
FAM126A	Q9BYI3	5	NAN	22.85	23.88	23.37	23.98	23.70	23.91	23.76	23.42	23.96	23.89	NAN
FAM134C	Q86VR2	3	22.65	22.36	23.19	24.42	24.24	24.35	22.45	22.85	22.28	22.99	22.26	22.60
FAM160B1	Q5W0V3	3	NAN	NAN	NAN	NAN	22.37	22.39	NAN	NAN	NAN	NAN	NAN	NAN
FAM162A	Q96A26	3	NAN	NAN	NAN	NAN	23.99	23.80	NAN	NAN	NAN	NAN	NAN	NAN
FAM210A	Q96ND0	3	22.91	NAN	23.67	24.57	24.19	24.48	NAN	NAN	NAN	NAN	NAN	NAN
FAM26E	Q8N5C1	3	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	23.91	24.02	23.67
FAM36A	Q5RI15	2	NAN	NAN	NAN	NAN	23.28	23.01	NAN	NAN	NAN	NAN	NAN	NAN
FAM3C	Q92520	5	NAN	23.40	NAN	NAN	23.81	23.89	NAN	NAN	NAN	NAN	NAN	NAN
FAM91A1	Q658Y4	12	24.60	24.67	24.46	24.30	24.32	24.43	24.22	24.36	23.73	24.96	25.32	25.02
FAM98A	Q8NCA5	15	24.62	26.07	25.42	26.09	26.05	25.95	27.93	27.31	27.89	27.16	27.82	27.15
FAR1	Q8WVX9	3	NAN	23.12	NAN	NAN	23.12	23.43	NAN	NAN	NAN	NAN	NAN	NAN
FARP2	O94887	8	NAN	NAN	NAN	NAN	NAN	NAN	26.10	25.90	25.15	NAN	NAN	NAN
FARSB	Q9NSD9	10	23.98	26.06	NAN	25.09	25.07	25.14	25.01	26.14	25.85	25.69	25.57	26.50
FARSLA	Q9Y285	5	23.71	24.31	NAN	23.20	23.57	23.45	23.17	25.24	24.39	23.61	24.25	24.18
FAS	P25445	5	23.33	NAN	24.87	23.28	22.97	22.87	NAN	NAN	NAN	NAN	NAN	NAN
FAS,FASN	P49327	95	28.91	30.10	28.06	29.59	29.76	29.87	27.39	28.42	28.12	27.83	27.46	28.12
FAT3	Q8TDW7	2	NAN	NAN	NAN	NAN	NAN	NAN	24.04	23.90	NAN	24.57	24.46	24.41
FAU	P35544	3	22.19	24.42	24.03	NAN	22.88	22.06	26.57	26.42	27.65	26.65	27.55	25.99
FBL	P22087	16	25.35	25.67	26.15	26.44	26.22	26.03	28.44	27.55	28.23	28.23	27.55	27.30
FBLIM1	Q8WUP2	5	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	23.96	24.08
FBLN5	Q9UBX5	2	NAN	23.77	NAN	NAN	23.83	NAN	NAN	NAN	NAN	NAN	NAN	NAN
FBXO21	O94952	2	NAN	NAN	NAN	NAN	23.85	24.07	NAN	NAN	NAN	NAN	NAN	NAN
FIP1L1	Q6UN15	4	NAN	NAN	NAN	NAN	23.81	23.83	NAN	NAN	NAN	24.46	NAN	23.72
FIS1	Q9Y3D6	3	NAN	23.44	NAN	NAN	24.63	NAN	NAN	NAN	NAN	NAN	NAN	NAN
FKBP10	Q96AY3	23	28.38	27.42	28.52	28.43	28.04	28.10	25.94	26.81	26.84	27.03	27.51	28.00
FKBP4	Q02790	8	NAN	24.52	NAN	NAN	25.48	26.00	NAN	NAN	NAN	NAN	23.88	24.26
FKBP9	O95302	16	25.67	27.32	25.87	27.30	27.43	27.30	24.30	25.71	23.89	26.81	26.31	27.08
FLOT1	O75955	18	NAN	26.07	24.61	22.67	22.52	20.52	27.73	27.28	27.60	26.23	26.11	26.58
FLOT2	Q14254	22	23.15	27.79	NAN	22.32	22.70	NAN	27.84	27.09	28.09	26.75	26.59	26.36
FMNL3	Q8IVF7	5	NAN	NAN	NAN	NAN	NAN	NAN	24.69	23.73	24.01	NAN	NAN	NAN
FMR1	Q06787	14	NAN	NAN	NAN	NAN	NAN	NAN	26.81	26.56	27.09	25.60	26.18	25.88
FNDC3A	Q9Y2H6	8	NAN	24.29	NAN	NAN	24.46	24.00	NAN	NAN	NAN	24.17	24.29	NAN
FTSJ3	Q8IY81	18	NAN	NAN	NAN	NAN	NAN	NAN	28.56	25.19	27.03	25.72	26.93	25.19
FUBP1	Q96AE4	8	NAN	24.07	NAN	NAN	23.73	23.54	NAN	NAN	NAN	23.64	23.14	23.43
FUBP3	Q96I24	12	24.43	24.54	24.77	25.46	25.42	25.37	24.41	24.00	24.42	24.37	24.41	24.39
FVT1	Q06136	3	22.65	22.83	22.78	24.29	23.90	23.82	NAN	NAN	NAN	NAN	NAN	NAN
FXR1	P51114	32	26.17	26.94	26.56	24.80	26.19	25.75	29.07	28.75	29.06	28.85	28.87	28.47
FXR2	P51116	23	NAN	25.24	NAN	NAN	23.76	25.14	28.57	27.01	27.73	27.70	26.78	26.23
G3BP	Q13283	12	24.65	24.65	24.77	25.75	25.93	25.47	26.86	26.63	26.80	26.38	26.34	26.47
G3BP1	Q13283	18	25.31	27.29	25.12	26.97	26.90	26.84	26.95	27.24	27.18	26.99	27.14	27.26
GAA	P10253	4	NAN	23.43	23.29	23.35	23.21	22.92	NAN	NAN	NAN	NAN	NAN	NAN
GAF1	Q9BXF6	5	NAN	NAN	NAN	NAN	NAN	NAN	23.76	23.19	24.15	23.11	23.22	NAN
GAK	O14976	5	23.27	24.65	NAN	24.14	23.97	23.92	22.83	NAN	23.26	23.62	23.51	23.84
GALK1	P51570	8	24.00	24.02	23.86	24.96	25.11	25.33	23.16	23.69	23.29	23.63	24.21	23.24

GALNT2	Q10471	12	25.66	25.06	25.65	26.23	25.93	25.61	24.64	25.33	24.51	25.03	25.62	25.67
GAPVD1	Q14C86	6	23.73	23.97	23.88	24.12	23.75	23.70	NAN	NAN	NAN	NAN	NAN	NAN
GART	P22102	19	26.48	27.40	25.70	25.79	26.00	26.51	25.34	25.45	25.72	25.03	25.68	25.55
GATAD2A	Q86YP4	4	NAN	NAN	23.00	24.10	23.12	23.16	NAN	NAN	NAN	NAN	NAN	NAN
GATAD2B	Q8WXI9	4	23.52	NAN	23.37	24.24	24.09	24.04	NAN	NAN	NAN	NAN	NAN	NAN
GBA	P04062	7	26.06	26.39	26.27	25.36	25.55	25.49	24.37	24.29	24.41	25.05	NAN	25.36
GDI1	P31150	9	NAN	NAN	NAN	NAN	23.42	22.95	NAN	NAN	NAN	NAN	NAN	NAN
GEMIN4	P57678	9	23.05	24.87	23.11	22.41	22.65	22.99	23.43	23.22	22.72	NAN	NAN	NAN
GEMIN5	Q8TEQ6	24	24.72	26.40	24.22	25.61	25.71	25.58	25.02	24.15	24.79	23.67	24.28	24.19
GFM1	Q96RP9	7	23.00	23.52	23.52	25.13	25.17	25.25	NAN	NAN	NAN	NAN	NAN	NAN
GFPT2	O94808	20	25.14	25.87	25.13	25.27	25.21	25.58	24.07	25.01	23.86	NAN	NAN	NAN
GGT7	Q9UJ14	5	NAN	NAN	NAN	NAN	23.21	23.28	NAN	NAN	NAN	NAN	NAN	NAN
GGYF2	Q6Y7W6	8	24.31	25.79	NAN	25.50	25.25	25.56	25.86	26.07	25.74	25.48	25.58	25.47
GIPC1	O14908	6	NAN	23.29	22.80	23.67	23.60	23.43	24.31	22.78	23.82	23.65	22.24	22.45
GIT1	Q9Y2X7	2	22.42	NAN	22.55	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
GJA1	P17302	13	NAN	23.16	NAN	NAN	22.92	NAN	26.58	25.62	26.30	25.29	25.54	25.24
GLIPR2	Q9H4G4	4	NAN	NAN	NAN	NAN	22.48	22.19	23.87	24.11	24.08	23.74	24.23	24.52
GLRX3	O76003	8	NAN	24.74	24.56	26.02	26.67	25.85	NAN	NAN	NAN	23.94	24.57	25.28
GLS	O94925	18	24.39	27.40	25.44	26.75	26.63	26.40	24.17	25.39	25.46	24.99	25.44	26.32
GMPPA	Q96IJ6	3	NAN	23.65	NAN	NAN	23.48	23.73	22.56	NAN	23.30	NAN	NAN	NAN
GMPS	P49915	10	NAN	24.06	23.29	24.47	24.44	24.82	22.87	23.45	23.12	23.18	23.29	23.60
GNA11	P29992	17	26.63	27.73	25.27	27.08	26.78	26.69	25.53	24.91	25.89	25.77	25.30	25.58
GNA13	Q14344	7	NAN	23.42	NAN	NAN	23.76	22.88	NAN	NAN	NAN	NAN	NAN	NAN
GNAI3	P08754	14	NAN	24.63	24.34	24.86	24.63	24.67	23.31	24.07	23.15	24.03	23.76	24.22
GNAQ	P50148	12	24.15	25.01	23.84	23.69	23.57	23.61	NAN	NAN	NAN	NAN	NAN	NAN
GNB2L1	P63244	31	28.48	30.14	30.07	29.43	30.06	29.80	33.37	33.01	33.45	32.74	33.25	32.54
GNL2	Q13823	11	NAN	23.53	NAN	NAN	23.32	23.82	25.57	24.42	25.45	24.76	24.97	24.56
GNL3	Q9BVP2	20	NAN	24.68	NAN	NAN	22.76	22.01	28.93	27.80	28.97	27.72	28.28	27.12
GNS	P15586	7	23.87	24.21	24.00	26.39	26.16	25.89	NAN	NAN	NAN	24.63	24.60	24.77
GOLPH3	Q9H4A6	5	NAN	24.66	NAN	NAN	23.19	23.24	22.36	23.29	22.80	22.41	22.97	22.97
GOLT1B	Q9Y3E0	4	NAN	26.28	25.79	25.19	24.42	24.54	25.20	24.82	25.58	24.08	24.32	24.43
GOPC	Q9HD26	4	22.13	NAN	22.66	23.40	23.51	23.36	NAN	NAN	NAN	NAN	NAN	NAN
GORASP2	Q9H8Y8	5	24.56	24.33	24.80	25.64	25.17	25.28	23.49	24.09	23.90	24.70	24.92	25.48
GOT2	P00505	9	23.80	24.02	NAN	25.94	26.12	25.88	NAN	24.21	24.31	24.53	24.54	25.59
GPC1	P35052	18	NAN	23.09	NAN	NAN	NAN	22.77	27.90	26.10	26.57	26.07	26.34	25.90
GPC6	Q9Y625	13	NAN	NAN	NAN	NAN	NAN	NAN	27.62	25.75	26.10	25.27	25.95	25.01
GPD2	P43304	19	25.37	26.18	25.81	26.40	26.41	26.21	24.01	NAN	24.55	24.65	24.03	25.44
GPI	P06744	11	23.43	25.77	23.87	26.21	26.57	26.67	23.43	24.71	25.09	23.80	25.67	26.02
GPR89B	P0CG08	3	NAN	NAN	NAN	NAN	NAN	NAN	23.57	NAN	22.97	NAN	NAN	NAN
GPS1	Q13098	12	25.30	24.91	25.70	26.61	26.66	26.57	23.62	24.98	22.27	24.53	23.51	24.92
GPX1	P07203	12	25.82	26.37	25.87	26.24	25.68	25.72	25.33	26.14	24.59	25.83	25.19	25.46
GRB2	P62993	5	23.63	23.17	23.61	23.52	23.55	23.71	22.31	22.70	22.74	NAN	23.25	23.58
GRHPR	Q9UBQ7	3	NAN	24.27	NAN	NAN	24.07	NAN	NAN	NAN	NAN	NAN	NAN	NAN
GRPEL1	Q9HAV7	4	NAN	24.19	24.14	25.20	24.96	24.83	NAN	NAN	NAN	NAN	NAN	NAN
GRSF1	Q12849	14	25.86	25.39	23.80	25.34	25.37	25.18	27.31	27.34	27.71	26.80	26.87	26.91
GRWD1	Q9BQ67	13	20.93	25.40	22.54	23.07	23.28	24.61	27.61	26.27	27.93	24.49	26.02	24.96
GSPT1	P15170	16	24.64	26.43	23.83	26.31	26.90	26.30	24.76	25.56	24.98	24.42	25.19	25.60
GSTK1	Q9Y2Q3	5	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	24.09	NAN	24.11
GSTO1	P78417	3	23.24	23.16	23.59	23.34	23.63	23.45	NAN	NAN	NAN	NAN	NAN	NAN
GTF2F1	P35269	2	NAN	NAN	NAN	NAN	23.37	23.38	NAN	NAN	NAN	NAN	NAN	NAN
GTF2H4	Q92759	3	NAN	NAN	NAN	NAN	NAN	NAN	23.49	22.68	NAN	22.68	25.25	NAN
GTF3C1	Q12789	9	NAN	26.28	25.33	24.74	24.48	24.39	24.39	24.00	24.37	24.42	24.17	24.40
GTF3C4	Q9UKN8	5	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	23.97	25.12	24.61
GTF3C5	Q9Y5Q8	5	22.18	21.89	23.22	23.96	24.12	24.24	NAN	NAN	NAN	NAN	22.71	22.91
GTPBP1	O00178	6	NAN	24.07	NAN	NAN	NAN	23.41	25.05	24.28	24.74	23.47	24.63	24.61
GTPBP10	A4D1E9	7	NAN	NAN	NAN	NAN	NAN	NAN	25.17	24.61	25.49	24.45	24.90	25.11
GTPBP4	Q9BZE4	22	NAN	23.41	NAN	NAN	23.81	22.67	28.30	27.28	28.78	26.91	27.56	26.53
GYS1	P13807	6	23.52	22.74	23.36	22.96	NAN	22.92	NAN	NAN	NAN	NAN	NAN	NAN
HABP4	Q5JVS0	6	NAN	NAN	NAN	NAN	NAN	NAN	24.90	25.20	25.07	24.60	25.62	24.44
HARS	P12081	4	NAN	NAN	NAN	NAN	23.90	24.10	NAN	NAN	NAN	NAN	NAN	NAN
HAT1	O14929	11	25.35	22.42	25.55	27.97	27.65	28.63	22.50	23.69	23.22	NAN	NAN	NAN
HBS1L	Q9Y450	8	NAN	23.94	NAN	NAN	23.89	24.72	24.22	23.97	24.18	NAN	23.56	23.49
HCFC1	P51610	4	23.28	23.21	NAN	22.73	22.44	NAN	22.28	22.62	22.19	22.85	22.90	23.37
HDGFRP2	Q7Z4V5	3	NAN	NAN	NAN	NAN	NAN	NAN	22.54	22.37	22.75	NAN	NAN	NAN
HEATR1	Q9H583	7	NAN	NAN	NAN	NAN	NAN	NAN	23.89	NAN	23.04	NAN	NAN	NAN
HEATR3	Q7Z4Q2	4	NAN	22.89	NAN	NAN	23.13	22.29	23.22	23.14	23.57	22.38	21.92	22.49
HEXA	P06865	5	NAN	NAN	NAN	NAN	23.86	23.91	NAN	NAN	NAN	NAN	NAN	NAN
HEXB	P07686	7	23.56	22.91	24.22	25.30	25.29	24.90	NAN	NAN	NAN	23.57	23.22	24.31
HIGD1A	Q9Y241	2	27.75	26.99	27.40	25.22	24.89	25.19	NAN	22.16	20.96	22.81	21.19	22.49
HIP1	O00291	10	NAN	NAN	NAN	NAN	NAN	NAN	24.71	25.18	24.54	24.59	23.90	23.59
HIST1H1E	P10412	10	NAN	NAN	NAN	NAN	NAN	NAN	21.58	22.15	22.26	NAN	NAN	NAN
HIST1H2BJ	P06899	6	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	23.34	23.47	23.19
HIST1H3A	P68431	4	NAN	NAN	NAN	NAN	NAN	NAN	25.63	25.99	25.88	23.82	23.81	23.07
HIST2H2AC	Q16777	9	NAN	NAN	NAN	NAN	NAN	NAN	23.62	22.68	23.61	NAN	NAN	NAN
HIST2H3A	Q71DI3	4	23.66	25.40	23.47	24.79	23.50	24.54	26.54	25.13	26.37	27.15	27.32	25.55
HK1	P19367	31	27.13	27.48	26.85	28.27	28.19	28.19	25.22	26.36	26.51	27.02	27.48	27.67
HK2	P52789	29	26.39	27.09	26.48	27.57	27.05	28.20	24.17	25.09	25.16	26.02	25.83	26.09
HLA-A	P01891	14	25.43	24.26	25.85	26.12	26.01	25.91	22.91	23.55	23.06	24.64	23.34	24.66
HLA-B	P30484	8	22.06	NAN	NAN	26.03	25.81	25.77	21.74	NAN	21.41	22.03	21.95	21.87
HLA-C	P04222	6	25.43	24.13	25.21	26.21	25.72	26.08	NAN	NAN	NAN	NAN	NAN	NAN
HLA-C	P10321	12	23.14	21.92	23.36	24.27	22.94	23.08	NAN	NAN	NAN	NAN	NAN	NAN
HLTF	Q14527	3	NAN	NAN	NAN	NAN	NAN	NAN	21.69	21.44	23.11	NAN	NAN	NAN
HM13	Q8TCT9	9	27.20	27.08	27.08	27.30	26.87	26.89	24.67	24.28	25.03	25.47	24.77	25.24
HMOX1	P09601	4	NAN	NAN	NAN	NAN	23.20	23.34	NAN	NAN	NAN	22.73	22.62	23.40
HMOX2	P30519	6	NAN	24.87	24.33	25.00	24.47	24.64	NAN	NAN	NAN	NAN	NAN	NAN

HNRNPA0	Q13151	10	24.74	25.04	25.25	26.03	25.96	25.73	25.81	25.42	25.13	25.50	25.40	24.85
HNRNPC	P07910	19	26.50	27.10	27.74	27.88	27.85	27.61	28.69	27.98	27.99	28.46	28.46	27.98
HNRNPDL	O14979	8	24.19	24.60	NAN	26.06	25.88	25.92	25.39	24.63	24.56	24.54	25.00	24.09
HNRNPL	P14866	23	26.95	27.93	27.24	27.68	27.53	27.47	28.73	28.24	28.45	28.08	28.31	28.12
HNRNPLL	Q8WVV9	9	NAN	24.29	NAN	NAN	25.08	NAN	25.69	25.15	25.77	24.44	25.16	25.14
HNRNPM	P52272	51	27.44	28.35	27.61	27.85	28.03	27.83	30.45	29.49	29.71	29.70	29.95	29.17
HNRPF	P52597	15	27.20	27.36	26.98	28.31	28.03	28.25	28.22	27.80	28.08	27.53	27.60	27.32
HNRPUL1	Q9BUJ2	25	24.46	26.05	23.49	26.06	26.16	25.07	28.41	27.48	28.14	27.72	27.57	27.56
HSD17B10	Q99714	17	30.24	28.16	27.64	28.19	27.78	27.79	27.81	28.24	28.14	27.24	27.63	27.80
HSD17B11	Q8NBQ5	6	23.49	24.09	23.64	23.88	23.65	23.46	23.11	NAN	22.76	NAN	NAN	NAN
HSDL2	Q6YN16	5	24.58	23.54	24.96	25.00	23.96	24.73	NAN	NAN	NAN	23.88	24.77	NAN
HSP90AA1	P07900	59	30.36	31.02	30.52	32.15	32.16	32.41	29.14	30.22	29.43	30.49	30.09	30.66
HSP90AB1	P08238	57	29.82	30.73	29.87	31.43	31.43	31.70	28.43	29.45	28.84	29.33	29.29	29.87
HSPA1B	P0DMV9	48	29.66	30.40	29.95	31.47	31.35	31.65	28.38	28.75	28.39	28.60	28.62	29.03
HSPA2	P54652	23	25.23	24.98	25.53	25.65	25.22	25.88	NAN	NAN	NAN	24.96	NAN	24.20
HSPA4	P34932	26	25.90	26.33	23.49	27.75	27.86	27.62	24.67	25.93	24.73	24.55	25.35	25.99
HSPA4L	O95757	10	NAN	24.94	NAN	NAN	23.72	23.76	NAN	NAN	NAN	22.92	23.01	22.97
HSPA8	P11142	50	31.33	31.55	31.22	32.19	32.33	32.41	30.97	31.29	31.05	31.05	30.84	31.23
HSPA9	P38646	35	29.27	29.43	29.34	30.28	30.21	30.30	28.19	28.79	28.17	29.20	28.93	29.24
HSPB1	P04792	21	30.79	31.23	31.15	30.02	30.03	30.11	29.57	30.02	29.51	29.40	29.75	30.12
HSPB6	O14558	5	25.33	26.52	26.38	25.08	24.95	24.58	24.58	25.26	25.41	24.10	24.56	24.99
HSPBP1	Q9NZL4	6	NAN	23.99	23.36	24.36	24.40	24.62	NAN	NAN	NAN	23.13	23.18	23.18
HSPD1	P10809	44	30.05	30.38	30.46	30.96	30.65	30.66	27.52	28.48	28.16	28.91	28.79	29.36
HSPE1	P61604	5	NAN	23.75	NAN	NAN	25.40	24.32	NAN	NAN	NAN	NAN	NAN	NAN
HSPH1	Q92598	38	28.97	28.45	28.71	29.63	29.60	29.95	27.16	27.48	26.93	27.83	27.53	28.01
HTRA1	Q92743	3	21.71	NAN	22.47	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
IARS2	Q9NSE4	11	24.81	24.99	24.31	25.11	24.50	24.82	NAN	NAN	NAN	23.34	22.97	22.93
ICAM1	P05362	8	26.07	25.17	25.82	25.10	25.02	25.22	NAN	NAN	NAN	NAN	NAN	NAN
IDH3A	P50213	4	23.66	25.12	24.49	24.88	24.45	24.71	NAN	NAN	NAN	NAN	NAN	NAN
IFI16	Q16666	21	NAN	24.92	NAN	NAN	23.83	23.26	26.81	26.38	27.37	25.63	25.68	25.56
IFRD2	Q12894	6	NAN	NAN	NAN	NAN	NAN	NAN	25.45	24.87	26.01	24.24	24.40	23.81
IGF2BP1	Q9NZI8	11	23.45	24.04	23.80	NAN	NAN	22.87	25.97	25.99	25.45	24.76	25.32	25.05
IGF2BP2	Q9Y6M1	18	24.01	25.38	24.08	22.17	23.46	23.61	27.60	26.85	27.42	26.65	27.24	26.75
IGF2R	P11717	65	27.95	27.64	27.07	28.51	28.40	28.60	26.00	26.55	25.85	27.52	26.39	26.93
IKBKAP	O95163	25	25.38	25.29	23.65	26.64	27.00	27.52	22.00	23.39	22.95	22.53	23.01	22.01
ILF2	Q12905	20	26.60	27.87	26.95	27.85	28.01	27.78	29.51	28.70	29.14	28.75	29.37	28.68
ILF3	Q12906	38	25.66	27.42	25.65	27.51	27.30	27.34	29.25	28.62	28.88	28.33	28.53	28.14
IMMT	Q16891	45	26.71	28.41	26.54	25.34	24.84	24.52	29.07	28.35	28.76	28.26	28.56	28.15
IMP4	Q8TCT7	3	NAN	NAN	NAN	NAN	NAN	NAN	24.40	23.78	24.09	NAN	NAN	NAN
IMPAD1	Q9NX62	3	NAN	23.79	NAN	NAN	24.40	24.41	NAN	NAN	NAN	NAN	NAN	NAN
IMPDH1	P20839	13	26.14	27.04	25.81	25.64	26.34	26.35	24.61	25.00	25.05	24.47	24.86	23.97
IMPDH2	P12268	25	29.07	29.72	29.43	29.17	29.30	29.61	28.21	28.58	27.87	28.44	28.66	28.63
INPP5K	Q9BT40	4	23.51	23.03	23.90	24.65	24.38	25.01	23.33	23.00	23.13	23.48	23.53	NAN
INPPL1	O15357	4	NAN	NAN	NAN	NAN	23.66	23.46	NAN	NAN	NAN	NAN	NAN	NAN
IPO11	Q9UI26	7	23.81	26.87	25.26	24.14	NAN	24.43	NAN	NAN	NAN	NAN	NAN	NAN
IPO4	Q8TEX9	18	25.88	27.08	26.54	25.46	25.37	25.54	25.28	24.73	25.18	24.21	24.51	24.31
IPO8	O15397	6	23.62	24.82	NAN	22.96	23.21	23.22	NAN	NAN	NAN	NAN	NAN	NAN
ISG15	P05161	4	23.83	NAN	24.42	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
ISLR	O14498	4	NAN	NAN	NAN	NAN	NAN	NAN	23.60	24.18	23.95	NAN	23.77	23.07
ITCH	Q96J02	3	NAN	NAN	NAN	NAN	22.91	23.39	22.79	22.66	NAN	NAN	NAN	NAN
ITGA2	P17301	13	23.51	25.83	22.83	24.63	24.72	24.24	NAN	NAN	NAN	24.16	22.89	23.39
ITGA3	P26006	5	NAN	NAN	NAN	NAN	22.70	22.18	NAN	NAN	NAN	NAN	NAN	NAN
ITPA	Q9BY32	2	NAN	23.90	NAN	NAN	NAN	22.70	NAN	NAN	NAN	NAN	NAN	NAN
ITPRIP	Q8IWB1	4	NAN	22.83	23.23	24.00	24.30	23.95	NAN	NAN	NAN	NAN	NAN	NAN
IVNS1ABP	Q9Y6Y0	22	27.33	26.75	27.32	27.74	28.18	28.51	25.37	27.24	26.08	26.41	25.42	26.95
IWS1	Q96ST2	3	23.52	NAN	NAN	22.37	22.60	22.55	NAN	NAN	NAN	NAN	NAN	NAN
KARS	Q15046	14	24.47	26.42	24.10	25.25	25.44	25.97	25.02	25.22	25.25	24.81	24.99	25.34
KCTD12	Q96CX2	4	NAN	23.46	NAN	NAN	23.15	23.47	NAN	NAN	NAN	NAN	NAN	NAN
KCTD17	Q8N5Z5	11	26.93	29.25	26.68	27.40	27.81	27.52	24.69	26.08	24.74	24.82	24.22	24.34
KCTD2	Q14681	10	24.99	26.55	26.03	25.48	26.01	25.83	22.88	23.54	23.49	23.23	NAN	23.86
KCTD5	Q9NXV2	15	28.94	30.03	29.59	30.17	30.11	30.35	27.14	28.12	27.08	28.16	27.25	27.75
KDELC2	Q7Z4H8	10	24.10	24.84	NAN	24.68	24.40	24.57	NAN	23.04	23.37	23.73	24.04	24.00
KDM1A	O60341	13	25.26	25.50	25.70	25.94	25.35	25.74	23.35	23.32	NAN	23.66	24.17	23.39
KEAP1	Q14145	11	23.15	23.65	23.16	24.46	24.57	25.45	22.81	22.99	23.44	NAN	NAN	NAN
KHSRP	Q92945	10	25.07	25.62	24.90	26.17	25.93	25.98	24.02	24.21	23.96	23.77	24.90	24.12
KIDINS220	Q9ULH0	20	NAN	24.91	NAN	NAN	23.27	21.30	28.75	26.70	28.88	26.56	27.90	25.63
KIDINS220	Q9ULH0	4	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	23.24	NAN	23.52
KIF23	Q02241	4	NAN	NAN	NAN	NAN	NAN	NAN	24.26	23.51	24.43	23.68	24.47	22.93
KIF2A	O00139	15	22.87	NAN	NAN	23.38	23.84	23.35	26.70	25.69	25.71	24.72	24.94	24.74
KLC2	Q6P597	10	NAN	22.01	NAN	NAN	22.57	22.98	NAN	NAN	NAN	NAN	NAN	NAN
KLF4	O43474	6	25.76	26.52	26.20	26.08	25.00	25.48	26.05	24.76	24.98	24.93	25.23	25.70
KPNA2	P52292	21	27.85	28.95	28.19	28.53	28.42	28.62	28.06	27.99	28.08	27.71	28.32	27.76
KRI1	Q8N9T8	6	NAN	NAN	NAN	NAN	NAN	NAN	25.28	24.05	24.53	24.77	25.19	24.81
KRR1	Q13601	7	NAN	22.80	NAN	NAN	24.17	NAN	26.10	25.51	25.73	25.74	26.19	26.07
LACTB	P83111	19	NAN	NAN	NAN	NAN	NAN	NAN	27.76	26.35	27.74	26.63	26.24	25.66
LAMB1	P07942	22	26.92	26.80	25.51	26.57	26.26	26.20	NAN	22.50	23.32	NAN	NAN	NAN
LAMP1	P11279	8	25.77	26.62	25.42	26.71	26.69	26.67	24.42	25.02	24.28	26.08	25.05	25.98
LAMP2	P13473	4	23.47	26.10	23.27	25.68	25.61	25.42	23.24	22.49	NAN	23.58	23.78	23.46
LAMTOR1	Q6IAA8	7	25.14	25.62	NAN	25.73	25.20	25.16	25.08	25.67	24.78	25.46	24.93	25.30
LAMTOR3	Q9UHA4	2	NAN	24.48	NAN	NAN	24.35	24.74	NAN	NAN	NAN	NAN	NAN	NAN
LAMTOR4	Q0VGL1	2	NAN	NAN	NAN	NAN	23.47	23.60	NAN	NAN	NAN	NAN	NAN	NAN
LANCL1	O43813	2	NAN	24.59	NAN	NAN	24.25	24.31	NAN	NAN	NAN	NAN	NAN	NAN
LAP3	P28838	8	NAN	24.20	NAN	NAN	24.07	23.99	NAN	NAN	NAN	NAN	24.68	24.90
LARP1	Q6PKG0	48	22.77	26.40	22.86	21.85	24.98	24.09	29.83	29.36	29.83	28.29	29.15	28.12
LARP1B	Q659C4	6	NAN	NAN	NAN	NAN	NAN	NAN	22.01	NAN	22.87	NAN	NAN	NAN

LARP4	Q71RC2	6	23.45	25.31	NAN	23.89	NAN	24.71	25.57	24.53	25.29	25.04	25.68	24.69
LARP4B	Q92615	10	NAN	24.80	NAN	NAN	24.75	24.02	25.64	24.24	25.27	24.74	25.79	24.04
LARP7	Q4G0J3	15	NAN	NAN	NAN	NAN	NAN	NAN	26.84	25.71	26.18	25.82	26.07	25.21
LAS1L	Q9Y4W2	7	NAN	NAN	NAN	NAN	NAN	NAN	25.16	23.82	25.17	NAN	24.85	24.68
LBR	Q14739	2	NAN	NAN	NAN	NAN	NAN	NAN	22.33	22.59	22.32	22.75	NAN	23.55
LCLAT1	Q6UWP7	3	22.69	23.99	22.78	24.09	23.74	23.77	NAN	NAN	NAN	NAN	NAN	NAN
LDHA	P00338	12	24.50	25.66	24.63	26.58	26.80	26.94	24.31	25.30	25.69	25.33	25.43	26.15
LDHB	P07195	3	NAN	NAN	NAN	NAN	23.17	23.29	NAN	NAN	NAN	NAN	NAN	NAN
LEMD3	Q9Y2U8	31	28.12	27.08	28.29	29.01	28.59	28.70	26.74	27.26	26.73	27.84	27.42	27.91
LETM1	O95202	17	25.33	26.62	25.79	26.97	26.33	26.43	NAN	24.53	24.67	24.72	23.97	25.02
LGALS3	P17931	7	23.85	25.08	24.14	26.93	26.96	26.63	24.60	25.47	25.15	24.90	25.07	25.59
LGMN	Q99538	2	NAN	NAN	NAN	NAN	24.01	24.05	22.08	22.19	21.98	NAN	NAN	NAN
LIG3	P49916	6	NAN	NAN	NAN	NAN	NAN	NAN	NAN	24.20	25.22	25.33	24.80	NAN
LLPH	Q9BRT6	3	NAN	NAN	NAN	NAN	NAN	NAN	26.67	25.46	26.47	NAN	NAN	NAN
LMAN1	P49257	20	27.55	28.31	27.96	28.45	28.35	28.22	26.62	27.45	26.66	27.11	26.60	27.17
LMAN2	Q12907	15	25.69	26.10	26.24	27.09	27.35	26.99	24.57	25.42	24.93	26.38	25.79	26.34
LNPK	Q9C0E8	4	23.07	NAN	23.37	23.43	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
LONP1	P36776	20	25.14	26.68	24.99	26.80	26.46	26.32	23.84	24.30	25.01	25.20	24.96	25.70
LONP1	P36776	13	NAN	21.60	22.12	21.32	22.39	21.26	27.65	26.16	27.42	26.76	26.78	26.09
LPCAT1	Q8NF37	8	25.83	25.41	25.88	25.49	25.47	25.49	23.75	24.13	23.70	24.31	24.28	24.59
LPCAT4	Q643R3	5	NAN	22.72	22.59	23.00	22.95	NAN	22.91	22.32	24.33	22.44	NAN	22.71
LRPPRC	P42704	96	29.38	32.38	28.91	30.42	30.16	30.10	28.79	28.93	28.74	29.29	29.06	29.33
LRRC15	Q8TF66	7	NAN	NAN	NAN	NAN	23.99	24.92	NAN	NAN	NAN	NAN	NAN	NAN
LRRFIP2	Q9Y608	14	NAN	25.75	NAN	NAN	23.65	23.34	27.06	25.68	26.98	25.47	25.59	24.90
LSG1	Q9H089	15	22.13	24.47	23.58	24.24	24.41	24.34	25.62	25.70	26.96	25.20	25.90	25.07
LSM14A	Q8ND56	3	NAN	NAN	23.10	24.01	23.91	23.57	NAN	NAN	NAN	NAN	NAN	NAN
LSS	P48449	5	NAN	23.48	NAN	NAN	23.66	23.99	NAN	NAN	NAN	NAN	NAN	NAN
LTN1	O94822	4	NAN	22.59	NAN	NAN	22.20	22.50	22.90	22.46	24.14	21.96	22.00	NAN
LTV1	Q96GA3	4	NAN	NAN	NAN	NAN	NAN	NAN	23.37	23.36	NAN	23.30	23.88	23.40
LUC7L	Q9NQ29	10	NAN	NAN	NAN	NAN	NAN	NAN	24.92	24.50	24.87	24.54	24.48	24.27
LUC7L2	Q9Y383	18	23.66	24.84	24.50	25.42	25.37	25.19	27.58	27.02	27.40	27.02	26.76	26.25
LUZP1	Q86V48	5	NAN	NAN	NAN	NAN	NAN	NAN	22.79	23.00	22.99	NAN	NAN	NAN
LYAR	Q9NX58	20	NAN	24.98	23.49	22.71	23.22	NAN	28.80	28.17	28.50	27.06	27.81	27.01
LYPLA1	O75608	3	23.20	NAN	NAN	23.10	23.77	23.84	NAN	NAN	NAN	NAN	NAN	NAN
LYRM4	Q9HD34	4	NAN	NAN	NAN	NAN	24.07	23.84	NAN	NAN	NAN	NAN	NAN	NAN
M6PR	P20645	3	NAN	NAN	NAN	NAN	24.91	24.87	NAN	NAN	NAN	NAN	NAN	NAN
MAGED2	Q9UNF1	7	23.60	23.33	24.05	23.85	24.55	24.13	NAN	NAN	NAN	NAN	NAN	NAN
MAK16	Q9BXY0	7	NAN	NAN	NAN	NAN	NAN	NAN	27.37	25.94	26.95	26.62	26.71	26.49
MAN1A2	O60476	3	NAN	22.75	NAN	NAN	23.42	23.07	NAN	NAN	NAN	NAN	NAN	NAN
MAN2A1	Q16706	6	NAN	24.27	NAN	NAN	24.69	23.78	NAN	NAN	NAN	NAN	NAN	NAN
MAN2B1	O00754	4	NAN	NAN	NAN	NAN	22.81	22.95	NAN	NAN	NAN	NAN	NAN	NAN
MANF	P55145	2	NAN	22.15	NAN	NAN	NAN	22.96	NAN	NAN	NAN	NAN	NAN	NAN
MAP1LC3B	Q9GZQ8	2	NAN	24.55	NAN	NAN	25.08	25.18	NAN	NAN	NAN	NAN	NAN	NAN
MAP1S	Q66K74	10	24.33	25.35	NAN	25.04	25.01	25.36	23.77	23.94	24.08	24.46	NAN	24.21
MAP2K3	P46734	7	24.95	25.75	24.64	24.51	24.39	24.84	23.32	23.99	25.12	NAN	NAN	NAN
MAP3K7	O43318	4	23.90	22.56	23.10	23.85	24.33	24.23	NAN	NAN	NAN	NAN	NAN	NAN
MAP3K7IP1	Q15750	20	26.42	23.82	26.36	27.04	27.87	27.68	NAN	25.69	24.98	25.97	25.96	26.21
MAP4	P27816	19	25.61	24.84	25.76	26.01	25.77	25.71	25.25	25.44	24.90	25.77	26.03	26.36
MAP4K4	O95819	12	NAN	23.79	NAN	NAN	23.95	NAN	23.93	23.80	23.90	NAN	NAN	NAN
MAP7D1	Q3KQU3	3	NAN	NAN	NAN	NAN	NAN	NAN	23.52	23.53	23.45	23.21	23.93	22.97
MAPK1	P28482	18	26.50	25.89	27.25	27.21	27.02	27.57	26.41	26.65	26.25	25.81	26.04	26.44
MAPK3	P27361	11	23.75	24.15	25.15	23.79	24.32	25.32	23.69	23.41	23.81	23.22	23.46	24.27
MAPRE1	Q15691	12	24.34	25.25	25.07	27.19	27.26	27.54	24.46	24.72	23.80	24.36	25.06	25.45
MARS	P56192	24	26.84	27.51	26.37	26.32	26.41	26.62	26.12	26.69	26.50	26.11	26.34	26.43
MAT2A	P31153	17	24.83	26.10	25.36	27.32	28.01	27.94	25.27	26.20	24.98	26.36	26.18	26.33
MAT2B	Q9NZL9	4	NAN	NAN	23.10	23.20	24.01	23.73	NAN	NAN	NAN	NAN	NAN	NAN
MBD2	Q9UBB5	5	NAN	NAN	23.58	24.63	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
MBD3	O95983	5	NAN	23.23	NAN	NAN	23.10	22.80	NAN	NAN	NAN	22.62	23.25	NAN
MBDin	Q9HCN4	2	NAN	NAN	NAN	NAN	22.87	23.61	NAN	NAN	NAN	NAN	NAN	NAN
MBNL1	Q9NR56	4	NAN	NAN	NAN	NAN	NAN	NAN	22.91	22.80	22.38	23.28	23.14	23.47
MCCC2	Q9HCC0	9	24.44	24.82	24.58	25.59	25.21	25.24	NAN	NAN	NAN	NAN	NAN	NAN
MCM5	P33992	32	26.64	27.33	26.71	27.95	27.98	28.38	26.73	27.49	26.78	27.67	27.02	27.46
MCM7	P33993	26	NAN	22.85	NAN	NAN	23.40	23.88	23.05	NAN	23.09	23.70	23.45	23.54
MCM7	P33993	31	26.95	27.63	27.11	28.34	28.44	28.47	27.96	27.49	27.52	27.98	27.91	28.11
MCMBP	Q9BTE3	4	NAN	NAN	NAN	NAN	23.68	23.62	NAN	NAN	NAN	NAN	NAN	NAN
MCU	Q8NE86	7	25.84	24.38	25.90	24.99	24.81	24.25	25.48	NAN	25.60	23.88	25.92	25.56
MDH2	P40926	18	27.13	27.04	27.44	28.60	28.16	28.26	24.94	26.58	27.14	27.17	27.48	28.11
MDN1	Q9NU22	10	NAN	24.17	NAN	NAN	NAN	23.82	NAN	NAN	NAN	NAN	NAN	NAN
ME2	P23368	9	NAN	25.48	NAN	NAN	23.73	24.00	NAN	23.73	22.71	23.67	22.73	23.73
MEPCE	Q7L2J0	9	NAN	NAN	NAN	NAN	NAN	NAN	26.22	25.74	26.03	25.04	26.22	25.61
MESDC2	Q14696	3	23.92	22.40	24.54	22.74	22.79	22.24	NAN	NAN	NAN	NAN	NAN	NAN
METAP1	P53582	13	NAN	24.96	NAN	NAN	24.14	23.26	28.69	28.16	27.93	25.06	26.69	26.33
METTL13	Q8N6R0	5	NAN	24.15	NAN	NAN	21.29	NAN	NAN	NAN	NAN	NAN	NAN	NAN
MGA	O43451	2	NAN	22.85	NAN	NAN	23.54	23.41	NAN	NAN	NAN	NAN	NAN	NAN
MGAT1	P26572	4	NAN	NAN	NAN	NAN	22.28	22.45	NAN	NAN	NAN	NAN	NAN	NAN
MGAT2	Q10469	5	23.49	22.73	23.87	24.64	23.98	24.21	NAN	NAN	NAN	NAN	NAN	NAN
MGEA5	O60502	6	NAN	23.95	NAN	NAN	24.60	24.60	NAN	NAN	NAN	NAN	NAN	NAN
MIB1	Q86YT6	2	NAN	NAN	NAN	NAN	NAN	NAN	20.65	20.60	20.48	NAN	NAN	NAN
MICAL1	Q8TDZ2	12	24.22	25.89	25.28	23.78	24.38	NAN	25.22	25.21	25.35	24.68	24.67	25.01
MICU1	Q9BPX6	3	NAN	24.05	NAN	NAN	22.44	22.35	NAN	NAN	NAN	NAN	NAN	NAN
MKI67	P46013	5	NAN	NAN	NAN	NAN	NAN	NAN	23.51	23.56	23.51	23.27	23.88	23.49
MLEC	Q14165	8	26.27	25.96	26.07	27.32	26.93	27.03	24.60	25.15	24.35	25.63	24.53	25.34
MLF2	Q15773	5	23.16	22.75	NAN	23.24	22.95	23.18	NAN	NAN	NAN	NAN	NAN	NAN
MMGT1	Q8N4V1	2	22.56	22.85	22.73	NAN	NAN	23.80	NAN	NAN	NAN	NAN	NAN	NAN
MMP14	P50281	7	24.17	24.82	24.57	25.03	24.97	25.38	NAN	23.96	23.58	24.68	24.01	NAN

MMS19	Q96T76	15	25.19	26.75	25.07	25.69	25.60	25.97	24.05	23.90	24.04	23.98	23.36	23.69
MOB1A	Q9H8S9	3	NAN	NAN	NAN	NAN	24.76	24.81	22.85	22.64	NAN	23.01	24.47	23.56
MOB2	Q70IA6	9	24.62	26.00	24.38	26.91	26.94	27.03	NAN	NAN	NAN	25.09	NAN	24.16
MOB4	Q9Y3A3	6	24.74	23.71	24.45	24.36	24.63	24.52	NAN	NAN	NAN	NAN	NAN	NAN
MON2	Q7Z3U7	4	NAN	24.51	22.58	22.86	23.29	23.96	NAN	NAN	NAN	NAN	NAN	NAN
MOV10	Q9HCE1	14	22.68	NAN	22.83	NAN	NAN	NAN	27.18	25.04	25.71	24.74	25.36	25.03
MOV10L1	Q9BXT6	5	NAN	22.38	22.50	23.37	23.52	23.61	22.10	22.10	22.40	NAN	NAN	NAN
MOXD1	Q6UVY6	26	26.39	27.98	25.68	26.20	26.51	26.44	29.05	28.93	28.69	29.15	28.73	29.16
MPDU1	O75352	2	25.03	26.02	25.27	24.71	24.56	24.27	NAN	22.58	22.04	NAN	NAN	NAN
MPHOSPH10	O00566	5	NAN	NAN	NAN	NAN	NAN	NAN	25.76	24.94	25.47	24.58	24.59	24.27
MRPL11	Q9Y3B7	2	NAN	NAN	NAN	NAN	22.15	22.34	NAN	22.04	22.26	NAN	NAN	NAN
MRPL12	P52815	8	24.15	24.21	25.03	25.74	24.64	24.65	23.23	23.24	NAN	NAN	NAN	NAN
MRPL38	Q96DV4	5	22.58	NAN	22.74	23.59	23.45	23.21	23.18	23.22	22.80	23.74	23.32	23.30
MRPL44	Q9H9J2	5	NAN	24.09	NAN	NAN	24.55	24.59	24.17	24.83	23.76	23.88	24.49	23.81
MRPL49	Q13405	3	NAN	22.50	NAN	NAN	23.09	22.76	22.08	NAN	22.28	NAN	NAN	NAN
MRPS17	Q9Y2R5	4	23.33	23.18	24.11	24.17	24.28	24.21	24.65	24.72	24.07	23.95	23.82	NAN
MRPS18B	Q9Y676	3	NAN	NAN	NAN	NAN	NAN	NAN	23.12	22.50	NAN	NAN	22.97	22.83
MRPS2	Q9Y399	5	NAN	NAN	NAN	NAN	22.95	23.17	23.62	23.11	23.44	22.76	23.44	22.74
MRPS23	Q9Y3D9	4	NAN	22.90	23.32	23.67	23.45	23.28	23.22	23.16	22.75	23.31	22.91	23.18
MRPS30	Q9NP92	4	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	21.99	21.61	22.25
MRPS31	Q92665	3	NAN	23.89	23.35	22.94	23.21	22.86	NAN	NAN	NAN	NAN	NAN	NAN
MRPS34	P82930	5	NAN	23.09	23.75	23.93	23.87	23.27	24.58	23.45	24.00	24.91	24.43	24.30
MRPS5	P82675	5	NAN	NAN	NAN	NAN	NAN	NAN	23.51	22.99	23.29	NAN	NAN	NAN
MRTO4	Q9UKD2	13	NAN	NAN	NAN	NAN	NAN	NAN	27.20	27.34	27.73	26.66	27.29	26.46
MSH2	P43246	16	22.48	26.56	23.63	26.06	24.90	26.20	22.12	22.74	22.09	24.07	22.54	21.50
MSH6	P52701	14	24.58	24.67	24.29	25.41	25.34	25.46	25.03	24.76	25.21	25.14	24.36	24.66
MTA3	Q9BTC8	11	22.69	NAN	22.45	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
MTCH1	Q9NZJ7	6	23.25	23.71	23.35	23.67	23.68	23.77	24.08	23.63	23.79	23.75	24.51	23.93
MTCH2	Q9Y6C9	12	26.99	27.00	27.80	27.59	27.15	27.07	27.03	27.38	27.12	27.49	26.86	27.63
MTDH	Q86UE4	25	24.58	25.28	25.22	25.79	25.77	25.53	28.20	28.17	28.35	28.30	28.27	27.63
MTHFD1	P11586	25	25.01	27.02	25.35	26.40	26.86	26.62	25.60	26.12	25.75	24.69	25.70	26.13
MTHFD1L	Q6UB35	30	26.49	27.35	26.40	27.89	27.77	27.81	26.85	26.87	26.99	27.27	26.99	27.45
MT-ND1	P03886	3	22.88	NAN	22.93	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
MTOR	P42345	3	NAN	22.99	NAN	NAN	22.10	22.15	NAN	NAN	NAN	NAN	NAN	NAN
MTPAP	Q9NVV4	8	NAN	NAN	NAN	NAN	NAN	NAN	26.54	25.87	26.33	25.23	25.74	25.55
MTX2	O75431	6	23.98	NAN	24.35	23.80	NAN	NAN	26.18	25.43	25.91	25.22	25.60	25.00
MX1	P20591	12	27.37	NAN	26.57	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
MXRA7	P84157	3	NAN	23.93	NAN	NAN	23.92	23.78	22.15	22.68	NAN	NAN	NAN	NAN
MYADM	Q96S97	8	26.07	29.26	25.57	24.56	23.79	23.09	28.87	28.35	28.47	28.51	28.55	28.59
MYBBP1A	Q9BQG0	62	26.82	28.74	26.82	27.48	27.52	27.34	30.58	29.51	30.37	29.67	30.10	29.08
MYC	P01106	17	28.45	27.93	28.93	27.30	26.52	26.59	25.67	24.32	25.40	24.27	24.41	25.47
MYCBP2	O75592	8	NAN	NAN	NAN	NAN	NAN	NAN	23.16	22.87	23.68	22.77	22.99	NAN
MYH10	P35580	195	29.81	31.27	27.00	27.43	28.11	28.22	32.52	31.94	32.52	31.26	31.62	30.77
MYL1	P05976	2	NAN	NAN	NAN	NAN	NAN	NAN	28.17	27.28	27.96	24.80	25.93	24.61
MYL6B	P14649	6	NAN	NAN	NAN	NAN	NAN	NAN	24.59	23.58	25.21	NAN	NAN	NAN
MYO10	Q9HD67	5	NAN	NAN	NAN	NAN	NAN	NAN	23.88	22.24	23.24	NAN	NAN	NAN
MYO9A	B2RTY4	3	22.58	NAN	22.21	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
MYOM1	P52179	2	NAN	NAN	NAN	NAN	NAN	NAN	23.29	NAN	23.75	NAN	NAN	NAN
NAA10	P41227	5	NAN	23.94	NAN	NAN	23.20	23.34	24.20	24.74	24.79	22.84	23.39	23.20
NAA15	Q9BXJ9	17	NAN	25.17	NAN	NAN	25.04	25.19	26.20	26.92	26.73	24.96	26.40	25.98
NACA	E9PAV3	8	24.75	27.25	25.53	26.60	26.89	26.51	28.21	28.41	28.58	27.68	28.41	28.31
NAGLU	P54802	4	NAN	NAN	NAN	NAN	22.44	22.48	NAN	NAN	NAN	22.91	22.89	22.85
NAP1L4	Q99733	16	25.66	25.25	25.73	26.15	26.39	26.44	26.44	26.35	26.81	26.00	26.00	26.02
NAPA	O96009	16	25.34	26.35	25.99	26.96	26.93	26.70	24.40	25.78	24.43	25.64	24.09	25.64
NAPG	Q99747	3	NAN	23.25	NAN	NAN	23.63	23.57	NAN	NAN	NAN	NAN	NAN	NAN
NARS	O43776	21	26.40	26.66	24.78	27.18	27.73	27.73	25.27	25.52	23.97	25.41	25.70	26.41
NASP	P49321	7	24.40	23.73	NAN	25.00	25.17	24.99	NAN	NAN	NAN	23.57	NAN	23.64
NAT10	Q9H0A0	40	23.07	25.44	NAN	22.18	21.90	22.04	29.38	27.69	28.74	27.71	28.50	27.16
NCBP1	Q09161	18	25.16	25.69	24.66	26.06	26.11	26.47	25.71	25.84	26.09	25.49	25.54	25.94
NCEH1	Q6PIU2	9	23.57	24.36	24.02	25.72	25.12	25.02	NAN	23.48	23.23	24.26	23.85	23.99
NCL	P19338	63	29.87	30.82	30.50	30.72	30.56	30.44	33.25	32.49	32.76	32.57	32.88	32.48
NCSTN	Q92542	7	24.22	24.37	24.38	25.35	25.21	25.67	23.70	24.26	23.66	23.56	NAN	23.94
ND2	P03891	2	NAN	NAN	NAN	NAN	NAN	NAN	22.87	NAN	23.39	NAN	NAN	NAN
ND4	P03905	4	24.34	NAN	NAN	23.32	NAN	NAN	23.89	24.06	24.77	NAN	NAN	NAN
ND5	P03915	3	23.96	22.88	24.21	24.48	23.74	23.93	24.42	24.36	24.80	NAN	NAN	NAN
NDUFA11	Q86Y39	3	NAN	23.49	NAN	NAN	23.66	23.74	NAN	NAN	NAN	23.37	NAN	23.70
NDUFA4	O00483	4	23.97	24.54	23.76	26.20	26.33	26.29	NAN	23.33	23.81	23.94	23.67	NAN
NDUFA5	Q16718	4	NAN	NAN	24.47	24.34	24.06	24.34	24.61	24.07	24.55	23.56	23.71	24.04
NDUFA8	P51970	6	25.03	24.36	25.72	25.49	25.00	25.12	24.62	24.66	24.68	24.52	24.70	25.24
NDUFAF4	Q9P032	3	23.80	22.59	22.99	23.60	23.36	23.93	NAN	NAN	NAN	NAN	NAN	NAN
NDUFB10	O96000	6	24.86	23.42	24.85	23.88	24.03	24.14	24.43	24.65	24.30	24.45	24.17	24.98
NDUFB11	Q9NX14	2	NAN	NAN	NAN	NAN	22.78	22.93	22.49	22.64	22.66	NAN	NAN	NAN
NDUFB3	O43676	2	22.69	NAN	NAN	23.15	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
NDUFB4	O95168	3	23.04	NAN	23.21	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
NDUFB9	Q9Y6M9	6	24.32	23.94	24.19	24.88	24.02	24.28	24.50	24.26	24.37	24.22	24.05	24.24
NDUFS2	O75306	14	25.71	25.11	25.94	26.19	25.85	25.97	25.65	25.86	25.79	26.04	24.99	25.24
NDUFS3	O75489	14	25.92	25.68	26.74	26.29	26.12	26.22	25.94	26.26	26.30	26.17	26.10	26.62
NDUFS5	O43920	4	22.80	23.42	NAN	23.67	22.96	23.05	22.48	NAN	22.79	NAN	NAN	NAN
NDUFS7	O75251	4	NAN	23.86	NAN	NAN	24.00	24.03	23.88	23.59	24.50	NAN	NAN	NAN
NDUFS8	O00217	6	25.29	24.59	NAN	25.35	24.96	24.83	24.83	24.86	25.05	25.02	25.18	25.07
NDUFV2	P19404	4	NAN	23.55	NAN	NAN	23.63	23.64	NAN	NAN	NAN	NAN	NAN	NAN
NEDD4	P46934	3	NAN	22.68	NAN	NAN	22.16	21.77	NAN	NAN	NAN	22.02	21.60	NAN
NELFB	Q8WX92	2	NAN	22.54	NAN	NAN	23.14	22.49	NAN	NAN	NAN	NAN	NAN	NAN
NELFCD	Q8IXH7	3	23.51	23.13	22.99	23.06	23.53	22.94	NAN	NAN	NAN	NAN	NAN	NAN
NEMF	O60524	16	23.25	23.02	22.28	NAN	23.61	NAN	26.70	26.99	27.45	25.17	25.69	25.08

NFIX	Q14938	2	NAN	NAN	NAN	NAN	NAN	NAN	22.83	NAN	22.69	NAN	NAN	NAN
NFKB2	Q00653	7	23.50	NAN	23.51	23.10	22.99	23.42	NAN	NAN	NAN	NAN	NAN	NAN
NFKBIB	Q15653	4	24.09	NAN	24.34	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
NFS1	Q9Y697	7	22.65	22.21	22.66	25.33	NAN	23.27	22.97	22.52	22.29	NAN	NAN	NAN
NGDN	Q8NEJ9	3	NAN	NAN	NAN	NAN	NAN	NAN	23.43	22.54	23.08	NAN	23.32	23.06
NHP2	Q9NX24	7	NAN	NAN	NAN	NAN	NAN	NAN	27.02	25.40	25.55	25.93	25.39	25.58
NHP2L1	P55769	4	22.48	23.52	22.36	23.16	23.16	23.29	24.62	24.31	24.55	NAN	NAN	NAN
NIFK	Q9BYG3	8	NAN	23.57	24.29	23.40	23.66	23.25	25.85	24.96	25.31	24.55	25.02	23.74
NIP7	Q9Y221	5	NAN	24.59	NAN	NAN	24.31	24.39	27.57	26.46	26.24	25.46	26.06	25.44
NKRF	O15226	8	NAN	NAN	NAN	NAN	NAN	NAN	23.57	23.30	23.50	23.63	23.69	23.59
NMD3	Q96D46	13	24.33	26.49	24.86	24.81	24.73	24.40	26.01	26.51	26.92	25.87	26.71	25.93
NMNAT1	Q9HAN9	10	NAN	NAN	NAN	NAN	NAN	NAN	26.73	25.52	26.76	25.86	26.75	25.03
NNMT	P40261	11	24.93	27.69	25.17	24.21	24.81	24.89	24.86	25.09	25.28	24.97	25.36	25.33
NNT	Q13423	8	23.06	24.89	23.81	24.99	24.59	24.43	23.55	23.85	24.01	23.89	NAN	24.06
NO66	Q9H6W3	5	NAN	NAN	NAN	NAN	NAN	NAN	21.55	22.18	22.19	NAN	NAN	NAN
NOB1	Q9ULX3	10	NAN	24.19	22.28	22.53	23.27	23.45	26.44	25.84	26.25	24.55	25.51	24.36
NOC2L	Q9Y3T9	21	22.50	25.04	24.31	23.34	23.99	24.23	28.13	27.08	27.79	26.93	27.55	26.81
NOC3L	Q8WTT2	13	NAN	23.58	NAN	NAN	21.93	21.86	28.05	26.44	27.67	26.23	27.36	26.14
NOC4L	Q9BVI4	28	27.98	28.04	28.36	29.06	28.64	28.46	27.08	27.24	27.14	27.87	27.49	27.00
NOL10	Q9BSC4	7	NAN	NAN	NAN	NAN	NAN	NAN	26.05	25.01	26.11	24.30	25.42	24.35
NOL6	Q9H6R4	38	NAN	25.27	NAN	NAN	21.99	21.80	29.30	28.98	29.69	28.02	28.44	27.16
NOL9	Q5SY16	10	NAN	24.59	25.34	24.03	24.64	NAN	26.67	25.45	26.59	24.88	26.31	25.53
NOLA1	Q9NY12	7	NAN	24.40	26.32	26.67	26.71	26.30	27.18	26.84	27.08	26.25	27.38	26.14
NOLC1	Q14978	3	23.26	24.05	23.37	23.23	22.89	22.58	23.82	22.84	24.12	22.55	22.69	22.30
NOM1	Q5C9Z4	5	NAN	NAN	NAN	NAN	NAN	NAN	24.14	22.95	23.17	NAN	23.72	23.35
NOP14	P78316	26	26.22	26.66	26.46	27.93	27.79	27.55	26.03	26.06	25.98	27.28	26.54	26.04
NOP16	Q9Y3C1	6	NAN	NAN	NAN	NAN	NAN	NAN	26.18	25.82	26.29	24.95	25.57	24.72
NOP2	P46087	21	NAN	23.24	NAN	NAN	24.07	NAN	28.23	27.42	27.63	27.50	27.69	27.01
NOP56	O00567	23	22.47	24.92	24.29	23.21	24.79	22.24	28.11	27.15	27.71	27.40	27.36	26.52
NOP58	Q9Y2X3	16	24.87	25.50	25.02	25.12	24.66	23.96	26.79	26.12	26.83	26.38	26.63	26.14
NOP9	Q86U38	9	NAN	NAN	NAN	NAN	NAN	NAN	26.19	24.53	25.87	24.39	25.62	24.22
NOSIP	Q9Y314	2	NAN	23.85	NAN	NAN	22.57	NAN	NAN	NAN	NAN	NAN	NAN	NAN
NPC1	O15118	3	NAN	22.35	NAN	NAN	22.91	22.82	NAN	NAN	NAN	NAN	NAN	NAN
NPEPPS	P55786	9	22.78	23.70	NAN	24.66	24.68	24.58	NAN	23.64	23.95	23.86	24.63	23.90
NPLOC4	Q8TAT6	14	23.07	23.98	23.32	25.36	27.06	26.65	22.70	21.79	23.29	23.84	22.36	24.56
NPM1	P06748	21	29.93	30.09	30.24	30.21	29.99	30.07	32.07	31.05	31.31	30.07	31.02	30.03
NPM3	O75607	3	23.68	24.54	24.07	25.03	24.88	24.82	25.38	24.70	24.78	25.43	25.25	24.86
NPTN	Q9Y639	5	25.38	25.32	25.69	26.57	25.99	26.38	23.78	24.11	23.85	24.74	24.08	24.67
NQO1	P15559	7	24.43	25.47	24.52	24.98	25.54	25.51	23.58	24.17	24.32	24.61	24.59	25.11
NRAS	P01111	6	NAN	25.18	24.93	25.24	25.45	25.49	24.42	24.62	NAN	24.59	24.11	23.98
NRBP1	Q9UHY1	4	25.66	26.38	23.86	24.12	24.37	24.39	NAN	23.12	23.29	NAN	NAN	NAN
NRD1	O43847	8	22.84	NAN	NAN	24.57	24.60	25.20	NAN	NAN	NAN	23.20	NAN	22.60
NRP1	O14786	17	23.79	25.03	23.17	25.97	24.57	23.50	27.59	26.25	27.52	26.21	26.67	26.48
NSDHL	Q15738	5	23.13	24.22	23.73	24.19	23.89	23.84	NAN	NAN	NAN	23.01	23.52	NAN
NSFL1C	Q9UNZ2	18	26.78	24.56	26.13	28.02	28.23	28.20	24.01	26.09	23.95	26.50	25.55	26.34
NSFL1C	Q9UNZ2	18	NAN	NAN	NAN	NAN	24.52	24.49	NAN	NAN	NAN	NAN	NAN	NAN
NSUN2	Q08J23	26	26.12	26.95	26.31	26.64	26.45	26.86	27.19	27.22	27.20	26.59	26.84	26.50
NSUN5	Q96P11	3	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	22.15	22.15	NAN
NT5DC2	Q9H857	7	NAN	24.34	23.28	25.26	24.83	24.48	NAN	23.64	23.14	23.72	NAN	23.85
NT5E	P21589	31	28.49	30.65	28.13	25.94	26.99	25.56	31.31	30.98	31.07	30.99	31.08	31.12
NTPCR	Q9BSD7	5	23.79	24.08	NAN	24.58	24.32	24.81	23.12	23.37	23.26	NAN	NAN	NAN
NUBP1	P53384	3	NAN	NAN	NAN	NAN	22.35	22.46	NAN	NAN	NAN	NAN	NAN	NAN
NUCB1	Q02818	15	24.55	25.57	24.85	27.55	26.37	26.69	NAN	NAN	NAN	21.20	NAN	21.38
NUCB2	P80303	5	23.26	23.75	NAN	25.13	23.73	23.62	NAN	NAN	NAN	NAN	NAN	NAN
NUDC	Q9Y266	8	22.95	23.52	23.72	25.21	25.42	25.48	23.53	23.67	23.12	23.76	23.23	23.91
NUDCD1	Q96RS6	7	NAN	23.34	23.92	24.45	24.69	25.23	NAN	NAN	NAN	NAN	NAN	NAN
NUDT16L1	Q9BRJ7	2	NAN	NAN	22.54	22.93	22.48	22.81	NAN	NAN	NAN	NAN	NAN	NAN
NUFIP2	Q7Z417	2	NAN	NAN	NAN	NAN	NAN	NAN	22.93	23.40	23.20	23.43	NAN	23.45
NUMA1	Q14980	3	NAN	NAN	NAN	NAN	NAN	NAN	20.83	20.88	20.92	NAN	NAN	NAN
NUMB	P49757	3	NAN	23.25	NAN	NAN	NAN	23.05	23.01	23.28	23.08	NAN	NAN	NAN
NUP188	Q5SRE5	12	25.06	25.86	23.06	23.65	23.79	24.10	NAN	NAN	NAN	NAN	NAN	NAN
NUP62	P37198	2	NAN	24.68	NAN	NAN	22.91	23.57	NAN	NAN	NAN	NAN	NAN	NAN
NUP93	Q8N1F7	20	23.28	26.88	23.81	27.31	26.57	26.74	NAN	NAN	NAN	23.20	23.44	NAN
NXF1	Q9UBU9	6	NAN	NAN	NAN	NAN	NAN	NAN	25.36	24.22	24.96	23.97	25.09	24.42
OAT	P04181	11	23.87	25.11	24.00	26.26	25.30	25.95	23.15	24.13	23.83	24.46	25.19	25.31
OCIAD1	Q9NX40	5	23.58	24.52	24.93	24.99	24.46	24.69	23.60	24.05	24.34	23.68	24.15	24.36
OCRL	Q01968	3	NAN	NAN	NAN	NAN	NAN	NAN	22.41	22.13	21.74	NAN	NAN	NAN
ODR4	Q5SWX8	9	23.59	23.43	24.13	24.97	24.54	25.27	NAN	NAN	NAN	NAN	NAN	NAN
OGFOD3	Q6PK18	10	23.06	24.53	NAN	23.23	23.38	23.44	NAN	22.45	22.35	23.26	23.11	22.31
OGT	O15294	6	NAN	NAN	NAN	NAN	NAN	NAN	24.50	24.21	24.39	24.13	24.93	23.75
OSTF1	Q92882	2	NAN	NAN	NAN	NAN	21.91	21.71	NAN	NAN	NAN	NAN	NAN	NAN
OTUB1	Q96FW1	6	NAN	23.43	23.04	24.22	24.52	24.51	NAN	NAN	NAN	NAN	NAN	NAN
OXA1L	Q15070	5	NAN	22.75	23.43	24.29	23.78	23.68	22.48	22.28	NAN	NAN	NAN	NAN
OXSR1	O95747	7	24.14	26.61	NAN	23.48	23.31	23.05	23.11	23.20	23.40	NAN	NAN	NAN
P13674	P4HA1	33	26.73	NAN	27.32	NAN	26.08	26.01	25.16	25.49	25.28	NAN	25.90	25.38
P4HB	P07237	54	34.30	31.59	34.36	32.53	32.26	32.38	29.79	30.30	30.12	31.34	30.79	31.51
PA2G4	Q9UQ80	29	25.04	27.82	25.13	26.46	26.76	26.54	28.31	29.01	28.72	27.67	28.10	28.44
PABPC1	P11940	33	27.74	29.55	27.54	28.39	28.56	28.42	29.32	29.14	29.10	29.41	29.64	29.41
PABPC4	Q13310	28	24.85	27.47	24.87	25.71	25.94	25.51	26.93	27.19	26.86	27.01	27.37	26.91
PAF1	P28328	10	24.06	24.00	24.36	26.14	25.93	25.77	24.26	23.44	23.28	NAN	NAN	NAN
PAFAH1B1	P43034	6	22.87	23.85	23.29	23.93	24.30	23.57	NAN	NAN	NAN	NAN	NAN	NAN
PAFAH1B2	P68402	2	NAN	24.16	NAN	NAN	23.13	23.00	NAN	NAN	NAN	NAN	23.42	23.67
PAICS	P22234	15	26.96	27.15	27.34	26.62	27.05	27.29	26.23	26.02	26.12	25.10	26.12	26.36
PAK1IP1	Q9NWT1	8	NAN	NAN	NAN	NAN	NAN	NAN	25.86	23.87	24.95	24.22	24.48	24.03
PAK2	Q13177	5	NAN	NAN	NAN	NAN	22.77	22.97	NAN	NAN	NAN	NAN	NAN	NAN

PAPSS1	O43252	5	NAN	NAN	NAN	NAN	23.52	23.42	NAN	NAN	NAN	NAN	NAN	NAN
PARK7	Q99497	5	23.58	24.91	NAN	23.33	23.59	23.25	NAN	NAN	NAN	NAN	NAN	NAN
PARP1	P09874	32	24.18	27.06	NAN	24.18	24.44	23.63	27.58	27.94	28.38	26.30	26.80	26.51
PARVA	Q9NVD7	5	NAN	26.24	NAN	NAN	24.00	23.58	24.07	24.43	24.53	23.61	23.77	24.57
PBRM1	Q86U86	2	NAN	NAN	NAN	NAN	22.75	22.49	NAN	NAN	NAN	NAN	NAN	NAN
PBXIP1	Q96AQ6	10	22.81	23.06	24.61	25.82	26.21	26.21	24.00	23.76	23.77	24.56	24.29	24.70
PC4	P53999	6	NAN	NAN	NAN	NAN	NAN	NAN	26.96	26.93	27.19	NAN	NAN	NAN
PCNA	P12004	10	25.46	24.97	26.14	27.46	27.62	27.52	24.60	25.53	24.58	26.25	24.91	26.39
PCOLCE	Q15113	8	NAN	NAN	NAN	NAN	NAN	NAN	24.71	25.32	24.93	24.46	25.02	26.06
PCYOX1	Q9UHG3	15	25.64	26.15	25.18	26.83	26.86	26.45	23.40	23.93	24.04	25.64	24.55	25.93
PDCD11	Q14690	62	NAN	23.82	NAN	NAN	20.46	20.76	30.34	29.22	30.03	28.70	29.02	28.24
PDCD4	Q53EL6	15	NAN	22.20	NAN	NAN	22.70	23.54	27.98	26.80	27.80	25.94	26.54	25.94
PDCD6	O75340	10	25.83	25.18	26.37	26.93	26.87	26.79	26.75	27.10	26.54	26.94	27.07	27.78
PDCL	Q13371	3	22.60	NAN	NAN	23.39	22.73	23.49	NAN	NAN	NAN	NAN	NAN	NAN
PDCL3	Q9H2J4	5	23.61	23.36	23.86	24.15	24.45	24.16	NAN	23.03	22.72	23.19	NAN	22.98
PDHB	P11177	5	NAN	22.62	22.44	23.72	23.10	NAN	NAN	NAN	NAN	NAN	NAN	NAN
PDIA3	P30101	7	NAN	NAN	NAN	NAN	26.71	26.95	NAN	NAN	NAN	25.96	25.91	26.54
PDIA6	Q15084	24	30.49	30.22	30.59	31.37	31.55	31.48	28.76	29.59	29.54	30.55	30.20	30.94
PDLIM5	Q96HC4	9	24.36	24.14	24.49	25.13	25.22	25.35	23.78	23.16	24.27	NAN	23.36	23.70
PDS5A	Q29RF7	3	NAN	22.89	NAN	NAN	23.33	NAN	NAN	NAN	NAN	NAN	NAN	NAN
PEBP1	P30086	6	24.12	24.43	24.34	25.17	24.89	25.35	NAN	NAN	NAN	NAN	NAN	NAN
PELO	Q9BRX2	8	22.66	23.44	NAN	23.13	23.37	23.51	23.04	24.13	23.04	23.34	23.02	23.63
PELP1	Q8IZL8	17	25.80	NAN	NAN	22.75	NAN	NAN	27.24	25.53	26.47	26.00	27.55	25.62
PES1	O00541	9	23.07	23.60	NAN	23.90	23.74	23.48	24.55	23.74	24.47	24.26	24.55	23.56
PEX5	P50542	7	23.76	23.30	23.71	23.05	23.51	23.28	23.58	23.48	23.59	NAN	NAN	NAN
PFDN2	Q9UHV9	2	21.57	22.81	NAN	24.51	24.41	24.48	22.04	22.27	22.03	22.00	21.87	NAN
PFKFB3	Q16875	28	26.88	27.70	27.51	28.09	28.27	28.55	25.22	26.35	24.88	26.96	26.16	26.81
PFKM	P08237	12	23.61	24.14	23.88	23.85	23.74	23.80	NAN	NAN	NAN	NAN	NAN	NAN
PFN1	P07737	13	26.58	27.58	26.67	28.93	28.81	28.60	25.29	27.49	26.98	26.99	27.12	28.29
PGAM5	Q96HS1	18	26.22	25.95	26.66	26.98	25.87	26.86	27.02	26.49	26.89	26.74	27.04	26.62
PGD	P52209	4	23.03	25.28	NAN	23.73	23.54	23.77	NAN	22.20	22.94	NAN	NAN	NAN
PGM1	P36871	5	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	21.11	22.12
PGM3	O95394	4	NAN	NAN	NAN	NAN	22.02	22.39	NAN	NAN	NAN	NAN	NAN	NAN
PGRMC1	O00264	11	26.88	26.61	27.68	27.64	27.11	27.32	25.35	25.81	25.57	26.59	26.03	26.50
PGRMC2	O15173	9	26.19	26.03	26.68	27.15	27.09	26.79	25.36	25.55	25.45	26.69	25.71	26.58
PHF5A	Q7RTV0	5	NAN	22.65	NAN	NAN	23.40	23.03	23.23	23.37	22.85	23.99	23.72	23.86
PHGDH	O43175	16	25.88	27.48	26.19	26.64	27.08	26.81	26.79	26.92	26.50	26.70	26.39	27.08
PHLDA2	Q53GA4	2	22.38	21.92	22.49	NAN	NAN	22.68	NAN	NAN	NAN	NAN	NAN	NAN
PICALM	Q13492	15	25.58	25.32	25.72	24.80	23.30	24.17	27.38	27.03	27.69	25.18	26.54	26.96
PIGK	Q92643	3	23.89	NAN	24.50	24.02	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
PIK3R4	Q99570	7	23.72	24.22	NAN	23.00	23.30	23.55	23.64	NAN	23.36	NAN	NAN	NAN
PIP4K2A	P48426	3	NAN	NAN	NAN	NAN	24.11	24.07	24.25	NAN	24.20	NAN	25.06	23.58
PIP4K2C	Q8TBX8	4	23.00	NAN	23.25	23.42	23.26	23.83	NAN	22.63	22.40	22.34	22.41	22.67
PITRM1	Q5JRX3	5	NAN	23.26	NAN	NAN	23.91	23.75	NAN	NAN	NAN	NAN	NAN	NAN
PLAA	Q9Y263	2	NAN	NAN	NAN	NAN	22.83	22.79	NAN	NAN	NAN	NAN	NAN	NAN
PLAT	P00750	5	NAN	NAN	NAN	NAN	23.20	23.20	24.46	23.83	23.88	23.81	23.94	23.70
PLAUR	Q03405	4	NAN	25.60	NAN	NAN	24.66	NAN	25.55	24.34	24.95	25.42	25.41	26.18
PLEKHO2	Q8TD55	4	NAN	NAN	NAN	NAN	24.17	23.96	23.80	24.08	NAN	NAN	NAN	NAN
PLIN3	O60664	13	24.82	25.64	24.90	26.72	26.78	26.66	24.59	25.00	24.89	24.97	23.64	25.66
PLP2	Q04941	2	NAN	23.13	NAN	NAN	24.15	23.96	NAN	22.97	22.38	23.62	23.12	23.60
PLXNB2	O15031	11	23.82	25.38	NAN	25.11	25.08	24.55	NAN	NAN	NAN	23.79	NAN	24.81
PMPCA	Q10713	3	23.84	25.38	23.93	25.11	24.97	24.70	23.44	23.41	23.90	23.81	23.97	24.83
PMPCB	O75439	6	22.50	22.31	23.03	24.45	23.68	23.17	NAN	NAN	NAN	22.88	22.57	22.98
PNN	Q9H307	3	NAN	NAN	NAN	NAN	NAN	NAN	25.92	26.08	NAN	NAN	NAN	NAN
PNO1	Q9NRX1	8	NAN	24.87	NAN	NAN	22.88	NAN	27.00	26.03	26.44	25.40	26.34	24.78
PNP	P00491	6	NAN	24.52	NAN	NAN	24.33	24.24	NAN	NAN	NAN	NAN	NAN	NAN
PNPT1	Q8TCS8	4	NAN	22.67	NAN	NAN	22.94	23.24	NAN	NAN	NAN	NAN	NAN	NAN
POLDIP2	Q9Y2S7	3	21.99	23.01	NAN	23.76	23.65	23.73	NAN	NAN	NAN	NAN	NAN	NAN
POLR1A	O95602	11	NAN	25.03	NAN	NAN	23.52	23.60	23.48	23.67	23.99	23.02	23.45	NAN
POLR1C	O15160	8	24.45	25.67	26.40	25.88	25.54	25.72	24.40	24.31	25.38	24.14	24.24	24.71
POLR1E	Q9GZS1	4	NAN	NAN	NAN	NAN	NAN	NAN	23.24	22.46	23.55	NAN	NAN	NAN
POLR3A	O14802	6	25.12	24.90	24.58	23.61	23.58	23.62	NAN	NAN	NAN	NAN	NAN	NAN
POLRMT	O00411	6	NAN	NAN	NAN	NAN	NAN	NAN	24.70	NAN	24.93	NAN	NAN	NAN
PON2	Q15165	9	25.95	25.70	25.74	26.03	25.39	25.27	24.81	24.75	NAN	24.97	24.44	25.02
POP1	Q8NE79	32	24.41	25.80	24.89	25.38	25.61	25.53	28.05	27.06	27.45	27.16	27.33	27.01
POP7	O75817	2	NAN	NAN	NAN	NAN	NAN	NAN	23.94	23.93	NAN	NAN	NAN	NAN
POR	P16435	18	24.46	26.74	24.67	26.14	26.11	26.27	24.36	25.06	24.26	24.80	25.36	23.40
POU5F1	Q01860	31	36.23	33.71	36.73	35.54	35.47	35.73	32.06	32.54	30.98	31.81	29.90	31.11
PPA1	Q15181	5	NAN	23.69	NAN	NAN	24.24	23.88	NAN	NAN	NAN	NAN	NAN	NAN
PPAN	Q9NQ55	15	NAN	22.79	NAN	NAN	22.63	NAN	28.10	26.59	27.62	26.55	27.24	25.81
PPFIA1	Q13136	3	22.56	22.73	NAN	22.67	23.37	23.37	NAN	NAN	NAN	NAN	NAN	NAN
PPFIBP1	Q86W92	6	NAN	NAN	NAN	NAN	23.18	22.75	NAN	NAN	NAN	NAN	NAN	NAN
PPIC	P45877	3	23.50	23.30	23.69	24.02	24.58	24.03	22.68	24.06	23.52	24.22	23.70	24.55
PPM1A	P35813	13	23.67	24.47	24.29	25.99	26.60	26.69	NAN	NAN	NAN	24.22	23.80	24.62
PPM1B	O75688	14	23.99	28.14	25.00	24.43	25.39	25.99	NAN	22.90	21.50	22.76	NAN	22.81
PPM1G	O15355	19	25.56	24.45	25.41	27.05	27.21	27.96	24.74	25.02	25.14	25.51	24.51	24.77
PPP1R12A	O14974	19	26.16	25.98	26.19	26.28	26.45	26.30	27.99	27.68	27.46	27.89	28.07	27.65
PPP1R18	Q6NYC8	11	NAN	NAN	NAN	NAN	NAN	NAN	26.23	25.73	26.44	25.75	25.49	25.77
PPP2CB	P62714	16	NAN	NAN	NAN	NAN	23.35	23.41	NAN	NAN	NAN	NAN	NAN	NAN
PPP2R1B	P30154	10	NAN	NAN	NAN	NAN	22.67	23.33	NAN	NAN	NAN	NAN	NAN	NAN
PPP2R2A	P63151	11	25.16	25.59	25.63	26.12	26.36	26.49	24.89	24.83	24.89	24.62	24.30	24.37
PPP2R5C	Q13362	5	NAN	NAN	NAN	NAN	23.51	23.45	NAN	NAN	NAN	NAN	NAN	NAN
PPP3CA	Q08209	7	22.94	23.08	23.96	25.42	25.69	25.37	NAN	23.07	22.63	23.89	23.06	23.80
PPP4C	P60510	9	24.63	NAN	25.11	26.26	26.20	26.39	NAN	NAN	NAN	24.95	NAN	24.38
PPP4R1	Q8TF05	7	24.44	24.71	24.09	23.23	23.81	23.60	23.15	23.66	23.29	21.99	23.16	23.15

PPP4R2	Q9NY27	6	24.04	NAN	24.74	25.07	24.90	24.81	NAN	NAN	NAN	NAN	NAN	NAN
PPP6C	O00743	12	26.59	26.42	27.04	27.08	27.30	27.47	25.74	25.73	25.82	25.32	25.54	25.77
PPP6R1	Q9UPN7	8	23.22	23.47	23.57	23.93	24.67	24.81	NAN	NAN	NAN	NAN	NAN	NAN
PPP6R3	Q5H9R7	15	23.17	23.42	23.79	25.53	25.46	26.86	22.85	24.55	22.96	NAN	NAN	NAN
PPT1	P50897	2	NAN	NAN	NAN	NAN	22.59	22.53	NAN	NAN	NAN	NAN	NAN	NAN
PRDX4	Q13162	19	29.54	29.41	30.14	30.19	29.80	29.90	27.08	28.02	27.04	28.29	27.70	28.11
PRDX6	P30041	18	27.01	28.53	26.36	28.06	28.55	28.27	24.96	26.67	26.79	26.16	26.92	27.63
PRKAA1	Q13131	4	NAN	24.30	23.21	24.18	23.56	23.77	NAN	NAN	NAN	NAN	23.52	23.12
PRKACA	P17612	5	22.70	23.40	23.97	24.54	24.68	24.58	23.54	23.53	23.96	23.79	NAN	24.54
PRKAR1A	P10644	10	24.80	25.72	24.81	24.86	25.41	25.30	24.84	25.09	25.21	24.62	24.83	25.08
PRKAR1A	P10644	8	24.72	25.16	24.51	24.39	25.30	24.93	23.36	24.30	24.27	24.47	NAN	24.52
PRKCD	Q05655	5	NAN	23.83	23.42	23.40	NAN	23.69	NAN	NAN	NAN	NAN	NAN	NAN
PRKCI	P41743	7	24.46	25.71	23.98	23.88	24.08	24.00	24.22	23.50	23.92	NAN	23.81	24.36
PRKCSH	P14314	23	27.44	27.57	27.78	28.53	28.33	28.30	25.40	26.23	25.81	27.03	26.18	26.78
PRKD1	Q15139	3	NAN	NAN	NAN	NAN	NAN	NAN	24.35	22.53	24.51	NAN	NAN	NAN
PRKRA	O75569	12	23.84	25.13	24.44	22.81	22.86	23.41	28.15	27.55	27.90	26.92	27.64	26.89
PRMT1	Q99873	22	27.79	27.59	28.05	29.18	29.02	29.09	26.79	27.27	26.99	27.31	27.46	27.52
PRNP	F7VJQ1	2	NAN	NAN	NAN	NAN	NAN	NAN	23.14	23.47	22.91	NAN	NAN	NAN
PROCR	Q9UNN8	3	NAN	NAN	NAN	NAN	24.28	23.96	NAN	NAN	NAN	NAN	NAN	NAN
PRPF19	Q9UMS4	14	26.36	27.36	26.85	27.59	27.40	27.45	27.08	26.89	26.83	27.01	27.26	26.78
PRPF4	O43172	17	25.47	25.77	24.85	25.44	25.43	25.32	27.15	26.67	26.92	26.71	26.87	26.15
PRPF40A	O75400	7	NAN	NAN	NAN	NAN	NAN	NAN	26.34	25.03	25.68	25.08	25.54	24.65
PRPF4B	Q13523	6	NAN	NAN	NAN	NAN	NAN	NAN	NAN	24.37	26.02	NAN	NAN	NAN
PRPSAP1	Q14558	10	24.71	25.77	24.41	24.99	25.74	25.67	24.04	25.42	24.45	24.72	24.71	24.96
PRPSAP2	O60256	12	21.89	26.17	22.69	24.13	25.04	24.73	23.52	24.80	23.52	22.08	NAN	22.30
PSAP	P07602	2	22.89	24.30	NAN	23.04	23.60	23.71	22.41	22.29	23.39	NAN	NAN	NAN
PSAT1	Q9Y617	5	NAN	22.49	NAN	NAN	24.19	23.42	NAN	NAN	NAN	22.94	23.09	23.30
PSMA3	P25788	11	25.49	25.18	25.21	26.07	26.30	26.38	23.37	24.46	23.33	24.82	24.31	24.88
PSMA5	P28066	9	26.35	27.38	27.62	27.58	27.42	27.53	23.88	25.59	24.61	25.70	25.08	25.59
PSMA7	O14818	14	27.48	27.71	27.68	28.29	28.11	28.27	24.12	26.75	24.93	26.19	26.05	26.42
PSMB3	P49720	10	26.20	26.61	26.60	27.19	27.42	27.21	24.31	25.30	24.04	25.57	25.21	25.75
PSMB8	P28062	2	NAN	NAN	NAN	NAN	23.49	23.53	NAN	NAN	NAN	NAN	NAN	NAN
PSMD9	O00233	4	23.71	23.72	23.38	24.25	24.48	24.53	NAN	NAN	NAN	23.05	NAN	23.26
PSME2	Q9UL46	5	23.98	NAN	24.03	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
PSME3	P61289	7	24.57	24.74	24.01	24.81	24.70	24.73	24.74	24.42	24.62	24.71	25.35	24.92
PSMF1	Q92530	2	NAN	NAN	NAN	NAN	22.20	21.97	NAN	NAN	NAN	NAN	NAN	NAN
PSPC1	Q8WXF1	3	NAN	25.10	NAN	NAN	24.61	24.39	NAN	NAN	NAN	NAN	24.13	24.14
PTBP1	P26599	26	28.31	29.38	28.83	28.87	28.77	28.49	30.25	30.21	30.40	29.90	30.05	29.82
PTDSS1	P48651	6	25.84	24.69	25.33	25.06	24.53	24.36	25.99	25.54	25.51	26.14	25.78	25.79
PTGES2	Q9H7Z7	2	NAN	NAN	NAN	NAN	23.25	23.29	NAN	NAN	NAN	NAN	NAN	NAN
PTGES3	Q15185	8	24.85	25.25	23.32	27.31	27.58	27.49	24.43	25.02	24.39	23.71	24.73	24.65
PTPN1	P18031	7	23.33	24.45	NAN	25.39	25.20	25.43	22.52	22.86	22.15	23.03	23.04	23.43
PTRH2	Q9Y3E5	6	25.24	26.52	25.37	26.63	26.05	25.81	26.70	26.01	26.03	25.54	26.51	26.43
PTS	Q03393	2	NAN	NAN	NAN	NAN	23.42	23.49	NAN	NAN	NAN	NAN	NAN	NAN
PUF60	Q9UHX1	17	21.16	24.01	24.66	25.47	25.74	25.24	28.55	27.99	28.58	27.94	27.71	27.81
PURB	Q96QR8	11	22.51	21.48	22.67	23.26	23.34	23.04	27.25	26.29	26.28	25.89	26.28	25.95
PVRL2	Q92692	3	NAN	NAN	NAN	NAN	23.54	23.16	NAN	NAN	NAN	NAN	NAN	NAN
PWP1	Q13610	14	NAN	24.20	NAN	NAN	NAN	23.21	28.49	27.52	27.54	26.11	26.20	26.20
PWP2	Q15269	4	NAN	NAN	NAN	NAN	NAN	NAN	24.38	23.31	23.99	23.66	23.97	23.39
PXN	P49023	2	NAN	NAN	NAN	NAN	NAN	NAN	23.44	23.32	23.73	NAN	NAN	NAN
PYCR1	P32322	6	24.77	24.40	25.80	25.82	25.68	25.72	24.79	24.72	24.49	25.30	25.39	25.59
PYCR2	Q96C36	6	23.66	23.50	23.79	24.15	24.06	23.97	23.00	23.40	22.47	NAN	NAN	NAN
PYCRL	Q53H96	4	23.40	NAN	23.63	23.78	23.47	23.48	NAN	NAN	NAN	NAN	NAN	NAN
PYGB	P11216	26	25.57	26.28	25.93	28.08	28.20	28.12	22.03	23.57	23.23	24.76	24.05	24.85
Q9Y6K5	OAS3	4	22.61	NAN	22.93	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
QSOX2	Q6ZRP7	16	26.63	26.07	26.98	26.80	26.36	27.09	23.56	23.51	22.69	23.58	23.40	24.24
RAB10	P61026	12	25.23	26.37	25.26	25.44	25.74	25.71	24.90	25.57	25.26	25.82	26.01	26.32
RAB11B	Q15907	15	25.30	26.49	25.57	26.91	26.98	26.73	25.11	25.70	25.13	26.70	26.19	26.83
RAB18	Q9NP72	11	24.36	25.53	25.19	26.63	26.26	26.14	25.47	24.93	24.35	25.01	25.02	25.29
RAB1A	P62820	12	27.01	28.34	25.99	27.41	27.86	27.69	26.04	26.93	26.93	27.23	27.13	27.28
RAB1B	Q9H0U4	12	NAN	25.09	NAN	NAN	24.56	24.35	24.26	25.01	24.70	23.76	24.63	24.66
RAB2	P61019	13	25.43	27.25	25.29	27.22	27.31	27.23	25.36	25.96	25.45	26.79	26.25	26.85
RAB32	Q13637	8	22.75	25.26	22.89	24.24	24.25	24.36	NAN	NAN	NAN	24.09	23.82	24.31
RAB34	P0DI83	8	23.40	23.64	23.57	24.61	24.52	24.80	23.52	23.75	NAN	23.57	NAN	23.67
RAB35	Q15286	4	25.39	24.39	24.89	23.70	23.48	23.32	22.28	22.80	22.44	23.56	22.57	23.68
RAB5A	P20339	7	22.41	23.41	22.53	23.96	24.13	23.95	NAN	NAN	NAN	NAN	NAN	NAN
RAB5B	P61020	7	NAN	23.59	22.35	24.39	24.02	24.53	23.83	23.04	23.13	23.39	23.82	23.77
RAB5C	P51148	10	26.36	27.12	26.59	27.59	27.46	27.61	26.18	26.87	26.40	27.09	26.60	27.12
RAB6A	P20340	7	NAN	26.68	24.98	27.80	27.75	27.50	25.27	25.52	25.35	26.06	25.48	26.24
RAB7A	P51149	15	25.90	27.82	25.72	27.85	27.61	27.51	25.92	26.60	25.73	27.13	26.73	27.28
RABL3	Q5HYI8	3	NAN	NAN	NAN	NAN	NAN	NAN	22.82	NAN	22.43	NAN	NAN	NAN
RAC2	P15153	7	22.27	22.43	NAN	24.52	24.47	24.58	22.16	22.47	22.35	22.08	21.91	22.39
RAD23B	P54727	3	NAN	24.24	NAN	NAN	24.10	23.95	NAN	NAN	NAN	NAN	22.60	22.71
RAE1	P78406	4	NAN	NAN	NAN	NAN	23.04	22.93	24.35	23.14	23.40	NAN	NAN	NAN
RALA	P11233	7	23.15	24.79	24.16	25.91	25.78	25.97	24.07	24.30	24.21	24.44	23.65	24.32
RAN	P62826	12	26.35	26.56	26.99	27.66	27.74	27.66	25.25	26.45	26.12	26.67	26.52	27.13
RANBP1	P43487	6	NAN	25.30	24.47	25.27	25.14	25.23	23.04	23.79	23.74	NAN	NAN	NAN
RANBP2	P49792	22	25.61	26.44	25.93	27.05	26.78	27.04	26.89	25.86	25.79	26.00	26.87	26.16
RANBP3	Q9H6Z4	2	NAN	NAN	NAN	NAN	22.48	22.58	NAN	NAN	NAN	NAN	NAN	NAN
RANGAP1	P46060	21	25.21	26.15	26.20	27.23	26.94	27.84	24.38	25.36	25.04	24.37	25.32	26.12
RAP1A	P62834	13	NAN	NAN	23.44	24.17	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
RAP1B	P61224	14	27.09	27.46	27.24	28.09	28.06	28.06	26.67	27.13	26.59	27.67	27.27	27.63
RAP1GDS1	P52306	9	24.79	25.93	24.83	23.50	24.12	24.83	NAN	NAN	NAN	NAN	NAN	NAN
RAP2C	Q9Y3L5	4	NAN	23.99	NAN	NAN	23.02	21.96	NAN	NAN	NAN	NAN	NAN	NAN
RB1	P06400	2	NAN	NAN	NAN	NAN	NAN	NAN	22.80	22.60	22.90	22.51	22.52	22.80

RBBP4	Q09028	20	28.51	27.07	28.47	29.27	28.99	29.14	27.23	27.42	27.03	28.01	27.33	27.70
RBBP5	Q15291	3	NAN	NAN	NAN	NAN	23.09	23.52	NAN	NAN	NAN	NAN	NAN	NAN
RBBP7	Q16576	19	27.63	26.38	27.74	28.58	28.18	28.48	23.68	25.48	26.04	25.27	26.17	NAN
RBM14	Q96PK6	12	23.37	23.54	23.58	24.72	25.09	25.12	25.01	24.16	24.24	24.75	24.65	24.09
RBM15	Q96T37	2	NAN	NAN	NAN	NAN	NAN	NAN	23.52	23.08	24.29	NAN	23.35	22.77
RBM19	Q9Y4C8	12	NAN	21.82	NAN	NAN	22.14	22.20	27.10	25.49	26.91	25.62	26.31	25.09
RBM25	P49756	8	NAN	24.02	23.84	25.05	24.30	24.48	25.14	24.65	24.86	24.77	24.75	24.26
RBM28	Q9NW13	20	NAN	22.87	NAN	NAN	22.10	NAN	28.03	26.29	26.63	25.92	27.16	24.89
RBM34	P42696	15	NAN	NAN	NAN	NAN	NAN	NAN	26.56	25.35	26.22	25.93	26.02	25.28
RBM39	Q14498	18	23.61	26.36	25.02	25.27	25.49	25.32	28.05	27.53	27.82	27.65	27.90	27.23
RBMS1	P29558	3	NAN	NAN	NAN	NAN	NAN	NAN	23.00	NAN	22.94	NAN	NAN	NAN
RCC1	P18754	3	NAN	22.03	NAN	NAN	23.75	23.36	NAN	NAN	NAN	NAN	NAN	NAN
RCL1	Q9Y2P8	11	24.26	23.95	24.59	25.84	25.83	25.93	25.98	25.30	25.32	25.97	25.57	24.93
RCN1	Q15293	17	26.43	28.49	27.63	28.71	27.65	28.24	23.37	23.60	24.34	24.89	26.07	26.01
RCN3	Q96D15	14	26.87	27.82	27.44	29.18	28.30	28.42	22.41	25.63	24.99	25.54	25.93	26.43
RCOR1	Q9UKL0	2	NAN	NAN	NAN	NAN	23.30	23.44	NAN	NAN	NAN	NAN	NAN	NAN
RDH11	Q8TC12	5	23.31	24.54	23.22	23.73	24.13	23.64	NAN	NAN	NAN	23.60	23.38	23.67
RDH13	Q8NBN7	7	NAN	23.57	22.53	23.40	22.56	23.34	NAN	22.65	22.22	NAN	NAN	NAN
RETSAT	Q6NUM9	9	24.38	24.63	24.15	25.20	25.13	25.11	23.91	23.61	24.15	23.99	24.18	24.00
REXO2	Q9Y3B8	2	NAN	NAN	NAN	NAN	NAN	NAN	NAN	22.73	22.26	NAN	22.89	22.86
REXO4	Q9GZR2	3	NAN	NAN	NAN	NAN	NAN	NAN	23.38	22.80	22.70	22.73	23.52	NAN
RFC1	P35251	10	NAN	NAN	NAN	NAN	NAN	NAN	25.98	25.70	25.65	25.02	24.51	24.23
RFC2	P35250	7	NAN	NAN	NAN	NAN	23.43	23.51	24.76	24.36	25.15	NAN	23.89	24.21
RFC3	P40938	9	NAN	24.20	23.21	24.62	24.46	24.13	26.17	25.24	26.40	24.58	24.79	23.98
RFC4	P35249	5	NAN	NAN	NAN	NAN	NAN	NAN	24.72	24.63	24.59	23.86	24.57	23.56
RFC5	P40937	10	NAN	24.01	NAN	NAN	23.77	23.70	26.57	25.70	26.95	23.88	25.29	25.06
RHOA	P61586	9	NAN	NAN	NAN	NAN	24.19	24.06	22.58	22.50	22.43	NAN	NAN	NAN
RHOT1	Q8IXI2	4	21.65	22.12	NAN	22.95	23.44	23.84	21.54	NAN	21.67	NAN	NAN	NAN
RHOT2	Q8IXI1	5	NAN	24.49	NAN	NAN	23.02	23.50	23.30	22.68	23.65	22.87	22.62	23.48
RIC8A	Q9NPQ8	6	23.28	24.24	NAN	23.12	23.50	23.89	NAN	NAN	NAN	NAN	23.37	23.11
RILPL1	Q5EBL4	4	NAN	NAN	NAN	NAN	23.01	23.17	NAN	NAN	NAN	NAN	NAN	NAN
RIOK1	Q9BRS2	19	27.06	26.51	27.00	26.36	26.34	26.65	24.83	26.32	24.93	24.32	25.27	24.31
RIOX1	Q9H6W3	5	NAN	NAN	NAN	NAN	NAN	NAN	24.48	23.87	24.46	23.84	24.32	23.45
RIOX2	Q8IUF8	4	NAN	NAN	NAN	NAN	NAN	NAN	23.72	23.54	23.47	NAN	NAN	NAN
RNF213	Q63HN8	13	23.55	NAN	NAN	23.12	23.21	23.22	NAN	NAN	NAN	NAN	NAN	NAN
RNH1	O60930	30	29.46	28.85	29.99	29.93	30.21	30.35	27.92	28.54	28.31	28.54	28.33	28.69
RNMTL1	Q9HC36	5	NAN	NAN	NAN	NAN	23.05	23.11	26.96	25.07	26.09	24.18	24.93	24.49
RP2	O75695	3	NAN	NAN	23.32	24.11	24.12	24.22	NAN	NAN	NAN	NAN	NAN	NAN
RPA2	P15927	3	23.65	NAN	22.66	25.17	24.56	24.95	NAN	NAN	NAN	NAN	NAN	NAN
RPAP3	Q9H6T3	4	NAN	NAN	NAN	NAN	24.08	23.71	NAN	NAN	NAN	NAN	NAN	NAN
RPF2	Q9H7B2	15	NAN	NAN	23.73	23.14	NAN	NAN	27.42	25.82	26.07	25.61	27.30	26.25
RPL10	P27635	18	26.80	27.89	27.97	26.48	27.37	26.94	31.52	31.62	31.76	30.64	30.78	30.42
RPL10A	P62906	23	26.20	27.78	27.63	26.85	27.62	27.40	31.20	31.36	31.76	30.67	31.10	30.55
RPL11	P62913	19	25.99	28.21	27.97	26.44	27.45	27.44	31.21	30.98	31.34	29.72	30.51	29.67
RPL12	P30050	14	27.45	28.97	29.04	27.98	28.75	28.39	31.97	31.80	32.08	31.29	31.76	31.39
RPL13	P26373	24	25.74	27.11	27.63	26.27	27.24	26.86	31.44	31.42	31.66	31.37	31.37	31.07
RPL13A	P40429	20	26.19	27.52	27.73	25.94	27.13	26.81	31.32	31.25	31.20	31.02	30.85	30.57
RPL14	P50914	10	26.59	27.98	28.26	26.59	27.58	27.06	32.08	31.80	32.05	31.38	31.63	31.17
RPL15	P61313	17	26.86	27.51	28.19	25.82	27.25	26.66	31.40	30.99	31.20	30.93	30.98	30.52
RPL17	P18621	19	26.91	29.04	28.76	26.23	27.96	27.09	31.94	31.87	31.90	30.59	31.44	31.07
RPL18	Q07020	12	26.68	28.03	28.13	26.46	28.08	27.22	32.23	31.78	32.03	31.55	31.82	31.22
RPL18A	Q02543	17	26.06	27.52	27.46	25.19	27.44	26.78	31.23	30.82	31.20	30.32	30.96	29.94
RPL19	P84098	16	24.70	26.63	26.33	25.91	26.49	26.03	30.23	29.97	30.24	29.80	29.78	29.27
RPL21	P46778	15	24.98	27.51	26.39	25.67	26.50	25.87	30.76	30.70	31.07	29.81	30.16	29.37
RPL22	P35268	10	25.46	26.59	26.97	26.44	27.08	26.51	30.65	30.59	30.89	29.95	30.23	29.87
RPL22L1	Q6P5R6	6	NAN	25.50	NAN	NAN	24.12	NAN	27.25	26.78	27.31	25.54	25.86	25.37
RPL23	P62829	12	27.48	29.16	28.48	27.61	28.03	27.70	31.52	31.71	31.87	30.91	31.28	30.72
RPL23A	P62750	19	27.22	27.00	28.45	27.48	27.67	27.02	30.43	30.37	30.63	30.43	29.90	30.02
RPL24	P83731	17	26.36	27.73	27.73	26.93	27.55	27.20	31.19	31.23	31.49	30.92	31.11	30.57
RPL26	P61254	17	23.18	26.17	25.65	24.36	24.76	24.57	30.29	30.65	30.24	29.42	29.43	28.93
RPL27	P61353	14	25.95	27.44	27.40	26.70	27.60	27.08	31.70	31.16	31.51	30.51	31.29	30.14
RPL27A	P46776	11	26.81	27.99	28.12	25.94	28.33	27.73	31.38	31.28	31.33	30.50	31.11	30.53
RPL28	P46779	17	24.69	25.95	26.70	24.06	25.91	25.22	30.53	30.28	30.35	29.85	30.03	29.48
RPL3	P39023	39	27.49	28.83	28.92	27.18	28.47	27.96	32.81	32.35	32.71	32.02	32.03	31.72
RPL30	P62888	10	26.11	27.16	27.40	26.17	27.30	26.79	31.86	31.30	31.67	30.74	31.12	30.58
RPL31	P62899	13	24.92	26.35	26.40	23.96	26.07	24.60	30.35	30.07	30.02	29.55	29.95	29.68
RPL32	P62910	14	25.02	27.51	26.28	25.19	25.96	24.91	31.09	30.33	31.21	28.75	29.08	29.11
RPL34	P49207	10	24.95	25.52	25.60	24.11	25.75	24.93	29.72	29.58	29.78	29.33	29.52	29.12
RPL35	P42766	9	24.40	26.57	25.66	24.80	26.28	25.36	30.58	30.43	30.51	29.08	30.42	29.65
RPL35A	P18077	14	24.27	25.36	24.99	23.05	24.95	24.16	29.29	29.41	29.44	28.91	29.12	28.54
RPL36	Q9Y3U8	7	24.33	25.56	26.21	23.44	24.87	24.21	29.71	29.60	30.23	28.23	28.89	28.24
RPL36AL	Q969Q0	12	NAN	NAN	NAN	NAN	NAN	NAN	24.88	25.15	25.21	24.53	25.02	24.42
RPL37	P61927	4	NAN	NAN	NAN	NAN	NAN	NAN	23.42	25.28	25.51	25.37	24.83	25.74
RPL37A	P61513	6	23.19	25.22	24.68	22.17	24.68	23.82	28.45	28.46	28.43	27.69	27.87	26.90
RPL38	P63173	7	24.76	28.13	26.49	25.20	26.02	25.59	29.41	29.85	29.91	29.35	29.76	29.24
RPL4	P36578	40	28.28	30.12	29.84	27.85	29.41	28.79	33.85	33.37	33.80	33.01	33.45	32.69
RPL5	P46777	30	26.80	28.40	28.40	26.91	28.16	27.67	32.56	32.23	32.44	31.73	31.92	31.19
RPL6	Q02878	25	27.71	29.20	29.51	27.26	28.84	28.21	33.26	32.82	32.99	32.78	32.99	32.36
RPL7	P18124	25	27.58	28.77	29.43	27.74	28.66	28.31	33.30	32.87	33.19	32.89	32.91	32.36
RPL7A	P62424	28	27.25	28.62	28.67	27.52	28.66	28.10	32.89	32.38	32.68	31.98	32.52	31.85
RPL7L1	Q6DKI1	4	NAN	NAN	NAN	NAN	NAN	NAN	24.94	24.04	24.53	24.03	24.80	23.61
RPL8	P62917	23	26.95	27.90	28.56	25.93	27.65	26.91	32.21	31.99	32.09	31.20	31.50	31.27
RPL9	P32969	19	26.82	28.50	28.13	27.56	28.40	28.00	32.15	32.13	32.20	31.27	31.80	31.32
RPLP0	P05388	22	28.36	29.29	29.69	28.95	29.77	29.45	33.34	32.99	33.29	32.48	33.09	32.55
RPLP1	P05386	7	24.19	28.14	27.65	26.71	27.54	26.84	32.06	32.23	32.52	30.85	32.31	31.47

RPLP2	P05387	11	25.05	27.58	27.12	26.72	27.27	26.32	31.62	31.04	32.07	30.06	30.92	30.62
RPP14	O95059	2	NAN	NAN	NAN	NAN	NAN	NAN	22.96	22.70	23.86	22.67	24.72	23.00
RPP40	O75818	4	NAN	24.79	NAN	NAN	NAN	23.15	25.28	23.94	25.63	23.18	25.05	23.93
RPS10	P46783	20	27.37	28.38	29.05	27.05	27.81	27.39	31.71	31.20	31.51	30.94	31.42	30.81
RPS11	P62280	20	27.52	27.71	28.54	26.84	27.62	27.07	31.66	31.46	31.82	31.18	31.41	30.89
RPS12	P25398	14	26.80	28.04	28.09	27.51	27.86	27.59	31.28	30.93	31.25	30.39	30.78	29.89
RPS13	P62277	16	27.24	28.39	28.93	27.06	27.96	27.82	32.62	32.45	32.69	31.94	32.29	31.60
RPS14	P62263	13	26.68	28.06	28.06	27.05	27.66	27.10	30.91	30.90	31.09	30.21	30.82	30.22
RPS15A	P62244	15	26.24	27.76	27.73	26.72	27.81	27.43	31.18	31.09	31.51	30.30	31.31	30.32
RPS16	P62249	21	26.78	28.36	28.48	27.49	28.14	27.67	32.10	31.85	32.08	31.62	31.68	31.31
RPS17	P08708	15	26.10	28.06	27.95	26.05	27.49	27.04	31.50	31.07	31.76	30.18	30.43	30.10
RPS18	P62269	23	26.79	28.85	28.63	27.66	28.40	27.98	31.82	32.00	32.06	31.62	31.90	31.34
RPS19	P39019	20	26.20	27.29	28.09	27.09	27.60	27.23	31.38	31.21	31.46	31.00	31.19	30.77
RPS2	P15880	20	27.40	28.64	29.28	27.55	28.41	27.99	32.12	31.88	32.03	31.62	32.04	31.39
RPS20	P60866	9	25.79	27.06	27.58	26.03	26.56	26.39	30.35	30.32	30.81	30.10	30.40	29.78
RPS21	P63220	7	NAN	24.31	24.72	24.57	24.94	24.71	28.20	28.24	28.40	26.53	27.55	26.53
RPS23	P62266	11	26.31	27.15	27.84	25.55	26.56	25.84	30.42	30.38	30.39	30.26	30.18	29.81
RPS24	P62847	6	25.38	27.43	27.24	25.25	26.04	25.22	30.50	30.40	30.45	29.18	29.54	29.16
RPS25	P62851	11	26.10	27.50	27.97	26.86	27.75	27.24	30.78	30.89	30.88	30.79	30.85	30.39
RPS26	P62854	6	25.92	26.89	27.05	25.27	26.40	25.60	30.07	29.70	29.99	29.56	29.80	29.23
RPS27	P42677	7	25.14	26.51	25.69	24.97	25.68	24.94	28.88	28.82	28.78	28.47	28.68	28.06
RPS27L	Q71UM5	6	22.28	25.13	NAN	24.12	24.23	23.90	26.62	25.65	26.18	25.45	26.15	25.19
RPS28	P62857	8	NAN	24.91	24.93	24.57	25.67	27.06	29.37	29.20	29.98	26.91	27.86	27.19
RPS29	P62273	4	21.73	24.24	23.49	22.46	22.86	21.70	26.59	26.52	26.71	25.63	25.85	25.42
RPS3	P23396	30	28.04	29.95	29.77	28.95	29.43	29.00	32.89	32.60	32.85	32.52	32.53	32.08
RPS3A	P61247	34	27.64	29.20	29.26	27.92	28.80	28.25	32.86	32.67	32.84	32.06	32.28	31.79
RPS4X	P62701	33	27.92	29.46	29.47	28.30	28.87	28.44	32.76	32.23	32.67	31.84	32.17	31.62
RPS4Y1	P22090	27	26.31	26.67	26.25	23.64	24.60	22.90	30.46	29.82	30.30	28.75	30.03	28.63
RPS5	P46782	20	28.31	29.15	30.14	27.92	29.00	28.57	32.63	32.73	32.83	32.58	32.68	32.29
RPS6	P62753	24	26.68	28.71	27.86	26.97	27.62	27.13	31.41	31.35	31.59	30.73	31.21	30.39
RPS7	P62081	19	29.02	29.95	30.30	28.17	29.39	28.67	33.75	32.85	33.78	32.18	32.84	32.34
RPS8	P62241	25	27.49	29.31	28.93	27.94	29.34	28.67	33.07	32.60	32.91	32.60	32.90	32.19
RPS9	P46781	27	27.27	28.76	28.74	27.74	28.43	27.95	32.22	31.93	32.14	31.80	31.98	31.35
RPSA	P08865	23	28.45	30.46	30.34	29.42	29.88	29.49	34.00	33.60	33.95	32.80	33.74	33.02
RQCD1	Q92600	6	NAN	NAN	NAN	NAN	NAN	NAN	24.02	23.77	24.98	24.93	24.62	24.78
RRAGA	Q7L523	5	22.47	24.34	24.38	23.90	23.78	24.05	NAN	NAN	NAN	22.85	23.76	23.01
RRAGC	Q9HB90	3	NAN	23.35	NAN	NAN	24.39	24.14	NAN	NAN	NAN	23.99	23.73	23.95
RRM1	P23921	6	NAN	24.39	NAN	NAN	23.42	24.22	NAN	23.45	23.23	NAN	23.54	23.45
RRP1	P56182	6	NAN	22.20	NAN	NAN	22.72	22.55	24.53	23.51	24.08	23.77	24.27	23.33
RRP12	Q5JTH9	48	24.19	27.73	25.65	25.78	26.28	25.87	29.00	28.29	28.75	28.25	28.78	27.83
RRP15	Q9Y3B9	4	NAN	NAN	NAN	NAN	NAN	NAN	24.52	23.96	24.16	24.02	24.43	NAN
RRP1B	Q14684	11	NAN	NAN	NAN	NAN	NAN	NAN	25.63	24.37	24.43	24.85	25.41	24.49
RRP7A	Q9Y3A4	11	NAN	NAN	NAN	NAN	NAN	NAN	27.04	26.47	27.46	26.63	26.47	25.46
RRP8	O43159	7	NAN	NAN	NAN	NAN	NAN	NAN	25.95	25.27	25.66	25.28	26.00	24.88
RRP9	O43818	12	NAN	25.36	NAN	NAN	24.86	24.16	25.71	25.77	26.15	25.57	25.79	25.88
RRS1	Q15050	12	NAN	NAN	NAN	NAN	NAN	NAN	27.18	25.68	26.60	25.74	27.15	25.08
RSL1D1	O76021	34	NAN	26.39	25.04	23.32	26.10	24.37	30.76	29.91	30.21	29.65	30.09	29.30
RSL24D1	Q9UHA3	2	NAN	NAN	NAN	NAN	NAN	NAN	NAN	23.14	22.77	NAN	NAN	NAN
RSU1	Q15404	12	24.77	27.72	26.26	26.11	26.29	26.06	25.04	25.82	26.55	24.58	25.33	26.50
RTCA	O00442	6	NAN	NAN	NAN	NAN	NAN	NAN	24.73	23.87	24.83	24.44	25.15	24.46
RTCB	Q9Y3I0	28	26.96	28.10	27.42	27.91	27.91	27.56	29.76	29.25	29.70	28.56	29.09	28.69
RTN3	O95197	4	24.20	NAN	NAN	25.22	24.31	24.79	NAN	NAN	NAN	NAN	NAN	NAN
RUVBL1	Q9Y265	26	29.09	29.04	29.31	29.65	29.46	29.68	28.03	28.17	27.60	28.27	28.29	28.11
RUVBL2	Q9Y230	30	28.31	28.17	28.73	29.02	28.84	29.02	26.83	27.26	26.90	27.31	27.10	27.34
S100A13	Q99584	3	NAN	NAN	NAN	NAN	NAN	NAN	24.06	25.40	25.25	NAN	25.29	24.31
S100A4	P26447	6	23.98	25.16	24.59	27.12	27.78	25.12	25.88	26.41	26.30	NAN	NAN	NAN
S100A6	P06703	4	26.72	27.85	28.14	27.88	27.99	27.52	27.09	27.63	27.71	26.84	26.98	28.16
SACS	Q9NZJ4	3	NAN	NAN	NAN	NAN	NAN	NAN	20.86	20.97	22.54	NAN	NAN	NAN
SAE1	Q9UBE0	4	NAN	24.81	NAN	NAN	23.29	23.14	NAN	NAN	NAN	22.06	22.29	22.21
SAMHD1	Q9Y3Z3	7	24.52	24.26	24.33	NAN	23.13	23.35	NAN	NAN	NAN	NAN	NAN	NAN
SAMM50	Q9Y512	14	NAN	NAN	NAN	NAN	NAN	NAN	26.54	25.38	26.34	26.37	26.62	26.12
SAR1A	Q9NR31	9	25.03	27.17	24.56	NAN	23.52	24.19	24.99	25.83	26.48	24.51	24.78	NAN
SARS	P49591	12	23.93	24.98	23.74	25.29	25.79	25.28	22.76	24.52	24.04	24.09	24.27	25.27
SART1	O43290	2	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	23.18	23.85	NAN
SBDS	Q9Y3A5	7	24.30	24.56	24.03	24.18	24.14	23.79	NAN	23.55	24.36	NAN	NAN	NAN
SCAMP3	O14828	2	22.77	NAN	NAN	24.74	23.70	23.95	NAN	NAN	NAN	NAN	NAN	NAN
SCCPDH	Q8NBX0	9	25.40	25.32	25.59	26.66	26.45	26.43	24.46	24.35	24.78	24.68	24.60	24.51
SCO2	O43819	4	NAN	NAN	NAN	NAN	23.85	24.50	NAN	NAN	NAN	NAN	NAN	NAN
SCUBE3	Q8IX30	2	NAN	NAN	NAN	NAN	NAN	NAN	21.10	20.79	20.98	NAN	NAN	NAN
SCYL1	Q96KG9	4	NAN	NAN	NAN	NAN	22.72	22.87	NAN	NAN	NAN	NAN	NAN	NAN
SDAD1	Q9NVU7	19	NAN	NAN	NAN	NAN	NAN	NAN	26.69	26.48	27.23	25.00	26.69	25.21
SDC4	P31431	3	NAN	NAN	NAN	NAN	NAN	NAN	22.29	21.45	21.64	21.80	NAN	21.24
SDF4	Q9BRK5	11	25.37	26.03	25.29	26.35	26.17	26.21	23.82	24.42	23.88	24.86	NAN	24.70
SDHA	P31040	19	26.85	26.67	27.55	27.59	27.22	27.21	24.86	25.16	25.96	26.09	25.07	25.62
SEC16A	O15027	8	24.88	25.90	NAN	24.52	24.19	24.54	25.33	24.41	25.46	23.91	23.75	24.37
SEC23IP	Q9Y6Y8	12	25.36	25.98	25.42	26.18	26.18	26.59	25.07	25.27	24.69	25.36	24.55	24.36
SEC24A	O95486	3	21.74	22.90	23.29	21.69	22.44	22.11	21.33	21.13	22.02	21.30	21.55	21.79
SEC24B	O95487	4	NAN	22.53	NAN	NAN	23.08	NAN	23.10	22.64	22.58	22.33	22.38	22.72
SEC24C	P53992	8	23.86	24.03	23.57	23.56	24.00	23.84	23.46	23.55	23.70	24.11	24.16	23.87
SEC24D	O94855	3	NAN	NAN	NAN	NAN	23.94	23.92	NAN	NAN	NAN	NAN	NAN	NAN
SEC61A2	Q9H9S3	11	NAN	NAN	NAN	NAN	NAN	NAN	NAN	22.20	23.27	21.97	22.02	22.36
SEL1L	Q9UBV2	19	27.29	26.20	26.89	27.57	26.83	27.16	23.00	25.24	23.54	25.19	NAN	26.14
SEMA3C	Q99985	2	NAN	NAN	NAN	NAN	NAN	NAN	22.58	22.06	22.30	NAN	NAN	NAN
SEMA7A	O75326	10	NAN	NAN	NAN	NAN	NAN	NAN	25.37	25.57	25.37	25.42	25.65	25.50
SERBP1	Q8NC51	22	25.61	27.25	28.34	25.91	26.84	26.73	30.02	30.17	29.83	29.75	29.72	29.57

SERPINB1	P30740	9	24.33	NAN	24.69	24.89	25.27	24.95	23.57	23.32	24.06	23.81	24.07	24.31
SET	Q01105	10	28.11	26.60	28.62	28.85	28.83	28.82	26.34	26.25	26.51	27.55	26.89	27.11
SETD3	Q86TU7	3	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	22.90	24.21
SF1	Q13285	7	23.98	25.40	23.99	24.23	23.90	NAN	23.81	23.46	23.97	NAN	NAN	NAN
SF3A1	Q15459	12	24.50	25.75	24.23	26.04	25.64	25.69	24.59	24.00	24.11	24.75	22.95	24.52
SF3A3	Q12874	16	24.24	25.85	24.22	25.51	25.57	25.25	24.53	24.35	23.71	24.67	24.89	24.86
SF3B2	Q13435	18	23.80	24.61	24.68	25.71	25.15	25.49	25.95	25.38	26.00	25.15	25.48	24.36
SFPQ	P23246	16	27.21	27.84	27.17	28.22	27.67	27.39	26.84	26.83	26.59	27.26	26.78	26.73
SFRS11	Q05519	5	NAN	23.61	NAN	NAN	24.00	24.20	25.95	25.35	25.60	26.12	24.94	25.59
SFRS3	P84103	7	NAN	25.56	NAN	NAN	24.42	23.74	27.74	27.28	27.96	27.73	27.96	27.45
SFRS4	Q08170	5	NAN	NAN	NAN	NAN	NAN	NAN	22.52	22.14	22.17	NAN	NAN	NAN
SFXN1	Q9H9B4	8	24.52	25.07	24.85	25.70	25.29	25.21	23.41	24.65	24.04	24.27	23.73	25.17
SFXN3	Q9BWM7	13	26.80	25.49	27.22	27.17	26.34	26.66	24.26	24.71	24.79	23.76	24.54	24.17
SFXN4	Q6P4A7	2	NAN	NAN	NAN	NAN	22.98	23.04	NAN	NAN	NAN	NAN	NAN	NAN
SGCE	O43556	2	NAN	NAN	NAN	NAN	NAN	NAN	20.28	20.53	20.55	NAN	NAN	NAN
SGPL1	O95470	5	NAN	NAN	NAN	NAN	23.20	23.02	23.26	NAN	23.18	NAN	NAN	NAN
SH3BP4	Q9P0V3	5	NAN	NAN	NAN	NAN	NAN	NAN	22.79	22.43	22.85	22.49	22.50	22.17
SHCBP1	Q8NEM2	5	NAN	22.88	NAN	NAN	22.76	23.20	NAN	NAN	NAN	NAN	NAN	NAN
SHMT2	P34897	21	25.11	26.87	25.13	27.83	27.65	27.69	27.00	27.50	26.96	26.41	26.81	27.45
SHOC2	Q9UQ13	5	NAN	NAN	NAN	NAN	22.86	22.84	22.36	22.65	22.75	NAN	22.71	23.11
SIGMAR1	Q99720	4	23.11	22.95	24.08	25.45	25.00	24.02	NAN	NAN	NAN	NAN	NAN	NAN
SIPA1L1	O43166	9	NAN	NAN	NAN	NAN	NAN	NAN	24.95	24.47	25.00	NAN	NAN	NAN
SIRT1	Q96EB6	12	25.79	24.68	26.01	26.01	25.71	26.56	NAN	NAN	NAN	NAN	NAN	NAN
SKIV2L	Q15477	35	23.81	26.06	22.68	21.77	22.72	22.22	28.65	28.40	28.48	27.31	28.13	27.74
SLAIN2	Q9P270	6	24.50	24.19	25.68	26.02	26.30	26.05	23.93	23.36	23.79	23.66	NAN	23.64
SLAIN2	Q9P270	6	23.37	24.47	23.79	25.90	26.23	25.92	NAN	NAN	NAN	23.53	NAN	23.96
SLC16A1	P53985	7	27.47	26.30	28.35	26.06	25.11	25.59	24.41	24.23	24.03	24.77	24.95	24.49
SLC16A7	O60669	3	22.62	NAN	23.77	21.81	21.96	21.77	NAN	NAN	NAN	NAN	NAN	NAN
SLC1A4	P43007	4	24.27	NAN	25.11	24.07	24.24	24.47	NAN	NAN	NAN	NAN	NAN	NAN
SLC1A5	Q15758	16	28.98	28.60	29.29	29.55	29.30	29.55	26.46	26.66	26.83	27.94	26.87	27.62
SLC25A11	Q02978	16	28.02	27.11	28.49	28.30	28.04	28.19	26.43	26.70	26.76	27.13	26.89	27.11
SLC25A12	O75746	23	27.11	25.41	27.48	27.05	25.76	26.84	22.74	23.11	20.90	24.32	22.50	23.58
SLC25A13	Q9UJS0	28	28.32	27.08	28.25	28.36	27.67	28.10	24.77	25.65	25.13	25.85	25.54	25.67
SLC25A20	O43772	7	23.26	23.12	23.87	24.47	23.98	23.71	NAN	23.06	22.95	NAN	NAN	NAN
SLC25A22	Q9H936	17	26.98	27.44	26.89	28.99	28.47	28.77	25.68	24.84	25.10	24.93	24.40	25.24
SLC25A24	Q6NUK1	10	NAN	26.58	23.91	24.94	24.51	24.50	23.54	24.63	24.49	23.58	23.56	24.61
SLC25A3	Q00325	18	30.25	29.51	30.78	30.49	30.15	30.37	28.94	29.27	29.49	28.74	28.53	29.02
SLC25A4	P12235	21	26.06	25.83	26.70	26.45	25.82	25.86	23.77	23.67	23.89	24.44	24.40	25.05
SLC25A5	P05141	24	28.82	28.12	28.97	29.13	28.63	28.91	26.67	27.33	27.14	27.65	27.26	27.56
SLC25A6	P12236	25	31.01	29.84	31.46	31.24	30.80	31.23	29.60	29.64	29.69	30.10	29.65	29.93
SLC27A3	Q5K4L6	2	NAN	23.64	NAN	NAN	22.30	22.33	NAN	NAN	NAN	NAN	21.95	21.99
SLC27A4	Q6P1M0	8	24.21	24.83	24.67	25.21	24.72	25.14	22.97	23.11	NAN	23.85	23.77	23.04
SLC30A1	Q9Y6M5	2	NAN	22.94	NAN	NAN	22.82	NAN	NAN	NAN	NAN	NAN	NAN	NAN
SLC30A7	Q8NEW0	3	24.59	24.65	25.31	25.47	25.35	25.25	23.46	23.66	23.02	NAN	NAN	NAN
SLC33A1	O00400	4	23.41	NAN	23.58	23.68	23.50	23.90	NAN	NAN	NAN	NAN	NAN	NAN
SLC38A5	Q8WUX1	3	23.44	23.25	23.21	24.04	23.38	23.65	NAN	NAN	NAN	NAN	NAN	NAN
SLC39A14	Q15043	3	24.01	24.18	25.14	25.26	24.61	24.64	NAN	NAN	NAN	23.99	NAN	24.35
SLC3A2	P08195	27	29.20	29.07	29.51	29.38	29.03	29.27	26.93	26.83	26.79	27.92	27.77	28.01
SLC4A1AP	Q9BWU0	4	NAN	NAN	25.22	24.82	24.38	24.85	23.35	23.20	NAN	23.33	NAN	23.55
SLC7A1	P30825	3	24.38	24.80	25.10	24.78	24.57	24.70	NAN	23.44	24.26	NAN	23.63	23.74
SLC7A5	Q01650	6	25.38	24.79	25.55	25.98	25.59	25.65	NAN	NAN	NAN	23.22	NAN	24.35
SLC9A3R2	Q15599	6	NAN	NAN	NAN	NAN	23.84	23.81	NAN	NAN	NAN	NAN	NAN	NAN
SLIRP	Q9GZT3	7	22.38	27.13	22.83	26.04	25.97	24.37	NAN	NAN	NAN	22.93	NAN	22.69
SLIT2	O94813	2	NAN	NAN	NAN	NAN	NAN	NAN	25.12	NAN	24.51	NAN	NAN	NAN
SMBP	Q9HD45	9	26.76	25.79	27.34	27.19	26.89	26.84	24.99	24.97	24.77	25.96	25.58	25.52
SMC1A	Q14683	17	24.23	24.61	NAN	26.01	25.31	24.60	23.85	NAN	23.29	22.54	NAN	23.07
SMC2	O95347	8	NAN	24.85	NAN	NAN	24.05	24.50	NAN	23.43	23.88	NAN	NAN	NAN
SMEK1	Q6IN85	24	26.32	23.96	26.10	27.34	27.04	27.63	24.38	25.37	24.45	25.73	24.70	25.33
SMN1	Q16637	3	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	23.38	23.97	NAN
SMTN	P53814	4	NAN	NAN	NAN	NAN	NAN	NAN	24.13	23.56	24.58	23.12	23.28	23.12
SMU1	Q2TAY7	7	NAN	22.17	22.49	23.74	23.13	23.12	22.86	22.90	22.75	23.36	23.37	23.23
SND1	Q7KZF4	82	28.57	29.74	28.97	29.78	30.02	29.78	32.44	32.18	32.29	31.99	32.24	31.88
SNRPC	P09234	3	NAN	NAN	NAN	NAN	NAN	NAN	23.90	23.14	24.23	NAN	NAN	NAN
SNRPE	P62304	5	25.88	27.21	25.27	25.10	25.34	25.05	26.58	26.62	26.96	25.37	25.73	25.29
SNRPF	P62306	3	NAN	25.43	23.92	24.84	24.45	25.11	26.43	26.78	26.60	NAN	24.95	24.82
SNRPG	P62308	3	23.07	25.07	23.13	NAN	23.43	NAN	26.12	25.56	26.40	24.42	NAN	24.92
SNX1	Q13596	2	22.26	NAN	NAN	23.36	23.32	23.90	NAN	NAN	NAN	NAN	NAN	NAN
SNX6	Q9UNH7	6	23.75	23.65	22.91	NAN	23.62	23.68	22.80	NAN	23.55	NAN	24.10	24.00
SOAT1	P35610	10	24.76	24.41	24.67	24.35	23.21	23.59	26.36	25.95	26.58	25.69	26.63	26.01
SOD2	P04179	2	NAN	NAN	NAN	NAN	23.17	22.78	NAN	NAN	NAN	NAN	NAN	NAN
SOGA1	O94964	5	NAN	NAN	NAN	NAN	23.61	23.23	NAN	NAN	NAN	NAN	NAN	NAN
SON	P18583	3	NAN	NAN	NAN	NAN	NAN	NAN	22.45	22.14	23.13	23.15	23.16	NAN
SOX2	P48431	12	28.02	25.90	28.28	26.29	25.60	26.22	22.65	23.34	23.11	24.85	24.13	23.67
SPATA5	Q8NB90	6	NAN	NAN	23.44	23.89	NAN	NAN	23.58	23.52	23.58	NAN	NAN	NAN
SPC18	P67812	6	24.93	26.04	25.30	25.87	25.97	25.76	23.67	24.90	24.83	24.62	NAN	24.78
SPCS3	P61009	3	23.31	24.26	23.76	25.28	25.11	24.28	NAN	NAN	NAN	23.92	NAN	24.84
SPFH1	O75477	17	21.84	25.20	NAN	21.91	NAN	20.85	28.49	26.07	28.21	26.75	26.62	25.74
SPNS1	Q9H2V7	5	26.74	26.65	26.95	25.23	25.15	24.93	NAN	NAN	NAN	22.12	22.23	22.60
SPTLC1	O15269	14	25.93	25.66	25.98	26.54	26.40	26.33	24.52	23.98	24.16	24.45	24.62	25.07
SQRDL	Q9Y6N5	12	24.41	24.00	25.02	25.75	25.92	25.81	NAN	23.67	25.00	24.53	NAN	24.65
SQSTM1	Q13501	7	23.05	23.78	23.54	23.60	23.34	23.41	23.57	23.36	23.41	NAN	23.56	23.68
SRBD1	Q8N5C6	3	NAN	NAN	NAN	NAN	NAN	NAN	24.29	23.22	23.66	NAN	NAN	NAN
SREK1	Q8WXA9	6	NAN	NAN	NAN	NAN	NAN	NAN	24.25	23.22	24.03	23.26	23.26	NAN
SRI	P30626	2	NAN	NAN	NAN	NAN	23.00	22.68	NAN	NAN	NAN	NAN	NAN	NAN
SRM	P19623	8	24.37	25.35	25.16	26.65	26.80	26.73	NAN	23.03	23.39	23.72	24.27	24.40

SRP14	P37108	9	25.21	25.21	25.61	25.96	26.15	25.88	27.66	28.20	28.44	26.69	26.69	26.87
SRP19	P09132	8	NAN	NAN	NAN	NAN	NAN	NAN	25.30	25.84	26.11	25.32	25.36	25.37
SRP54	P61011	23	25.93	25.19	24.89	25.24	25.68	25.32	27.22	28.01	28.89	26.41	27.19	26.71
SRP68	Q9UHB9	33	27.17	27.14	25.61	26.37	26.65	26.79	28.64	28.84	29.28	28.62	28.94	28.65
SRP72	O76094	38	27.07	26.93	23.23	26.64	26.99	26.47	29.26	29.20	29.32	28.64	29.05	28.84
SRP9	P49458	4	NAN	NAN	NAN	NAN	24.80	24.63	25.28	24.94	24.87	24.64	24.81	24.58
SRPK1	Q96SB4	18	NAN	NAN	NAN	NAN	NAN	NAN	29.01	28.17	27.32	26.91	28.13	26.24
SRPK2	P78362	12	NAN	NAN	NAN	NAN	NAN	NAN	26.44	26.33	26.67	25.87	26.04	24.38
SRPRB	Q9Y5M8	20	26.97	26.92	27.28	28.29	28.19	28.06	27.11	26.98	27.09	27.43	27.35	27.64
SRRM1	Q8IYB3	16	NAN	24.96	NAN	NAN	22.98	NAN	26.59	26.34	26.90	26.29	24.91	24.57
SRRM2	Q9UQ35	9	NAN	NAN	NAN	NAN	22.32	22.55	23.93	23.97	23.71	23.58	23.69	23.63
SRSF1	Q07955	14	NAN	24.78	NAN	NAN	23.41	22.62	27.90	27.20	27.11	27.45	27.37	26.38
SRSF2	Q01130	7	NAN	24.46	NAN	NAN	23.27	22.74	26.59	25.73	26.24	26.50	26.29	25.38
SRSF5	Q13243	6	NAN	NAN	NAN	NAN	NAN	NAN	26.40	25.32	26.21	25.13	25.89	24.98
SRSF6	Q13247	9	NAN	23.57	NAN	NAN	23.37	NAN	26.94	26.09	26.28	27.16	26.95	25.85
SRSF7	Q16629	8	NAN	25.90	NAN	NAN	23.74	23.59	26.75	25.33	25.63	26.86	26.13	25.51
SRSF9	Q13242	9	NAN	NAN	NAN	NAN	NAN	NAN	26.22	25.42	26.18	25.85	26.05	25.35
SSBP1	Q04837	6	25.01	24.40	26.09	26.59	25.88	26.28	23.48	24.48	23.66	24.93	24.36	25.01
SSR1	P43307	4	27.70	26.80	28.37	28.60	27.96	28.24	26.80	27.24	27.18	27.58	27.03	27.06
SSR3	Q9UNL2	3	27.03	26.59	27.48	26.97	27.16	26.66	26.47	27.10	26.70	26.65	26.99	27.07
SSR4	P51571	6	28.13	27.24	28.56	29.13	28.55	28.80	27.52	28.16	27.33	28.27	27.58	28.04
SSRP1	Q08945	25	24.27	26.02	24.59	25.45	24.95	25.00	28.40	27.20	27.64	27.44	27.96	27.46
ST13	P50502	4	NAN	24.27	NAN	NAN	25.30	25.58	NAN	NAN	NAN	NAN	NAN	NAN
STAG2	Q8N3U4	6	22.72	23.37	22.90	23.34	23.12	22.78	NAN	NAN	NAN	NAN	NAN	NAN
STAT3	P40763	21	26.54	27.84	27.06	26.38	26.27	26.70	24.34	25.18	25.42	24.35	24.37	24.52
STAU1	O95793	26	NAN	25.14	23.11	23.82	24.88	23.54	28.95	27.72	28.28	27.70	28.50	27.69
STAU2	Q9NUL3	8	NAN	NAN	NAN	NAN	NAN	NAN	23.59	22.81	23.16	22.90	23.29	NAN
STIP1	P31948	22	24.07	25.64	24.20	27.64	27.86	28.56	19.26	22.99	22.42	22.97	23.43	23.89
STK24	Q9Y6E0	6	NAN	NAN	23.15	23.38	24.06	23.64	23.09	23.65	NAN	NAN	NAN	NAN
STK38L	Q9Y2H1	16	25.47	27.34	25.23	27.25	27.57	27.65	NAN	NAN	NAN	24.66	24.34	24.37
STK39	Q9UEW8	7	NAN	25.34	NAN	NAN	23.58	NAN	NAN	NAN	NAN	NAN	NAN	NAN
STOM	P27105	15	29.29	29.58	29.63	26.96	26.95	26.67	29.78	29.06	29.55	29.46	29.42	29.56
STP1	P50225	6	NAN	NAN	NAN	NAN	NAN	NAN	24.45	24.30	24.31	24.01	24.08	NAN
STRAP	Q9Y3F4	20	25.78	26.34	26.25	26.74	27.15	27.06	26.19	26.18	26.04	26.23	26.27	26.57
STRIP1	Q5VSL9	5	25.03	24.82	24.90	23.53	23.43	23.54	NAN	23.92	23.12	23.68	NAN	24.33
STRN	O43815	4	23.77	23.05	24.06	23.76	23.65	23.29	NAN	NAN	NAN	NAN	NAN	NAN
STUB1	Q9UNE7	5	22.85	23.36	NAN	24.13	23.59	24.38	NAN	NAN	NAN	NAN	NAN	NAN
STX12	Q86Y82	5	22.68	23.78	23.21	25.47	25.25	24.97	22.85	22.96	22.83	23.67	23.08	23.32
STX16	O14662	2	NAN	NAN	NAN	NAN	22.76	23.09	NAN	NAN	NAN	NAN	22.19	22.39
STX7	O15400	4	NAN	NAN	NAN	NAN	24.37	23.90	NAN	NAN	NAN	NAN	NAN	NAN
STXBP1	P61764	2	NAN	23.28	NAN	NAN	NAN	22.16	NAN	NAN	NAN	NAN	NAN	NAN
STXBP3	O00186	6	23.48	24.88	22.08	22.98	23.57	23.56	21.94	22.57	22.64	23.22	22.08	23.57
SUFU	Q9UMX1	3	NAN	NAN	NAN	NAN	23.57	23.84	NAN	NAN	NAN	NAN	NAN	NAN
SUGP2	Q8IX01	9	NAN	NAN	NAN	NAN	NAN	NAN	24.64	23.87	24.20	24.11	24.57	24.03
SUI1	P41567	5	NAN	NAN	NAN	NAN	NAN	NAN	26.55	26.24	NAN	25.54	25.28	26.16
SUPT16H	Q9Y5B9	34	22.60	26.25	21.92	25.16	24.75	24.25	28.83	27.51	28.40	27.37	27.76	26.94
SUPT5H	O00267	14	23.72	23.41	22.81	26.95	26.15	26.63	25.00	24.47	24.38	24.90	24.78	24.47
SURF6	O75683	9	NAN	NAN	NAN	NAN	NAN	NAN	25.53	25.15	25.61	24.71	25.85	25.27
SYNCRIP	O60506	34	NAN	NAN	NAN	NAN	NAN	NAN	23.00	22.83	22.55	NAN	NAN	NAN
TAF9	Q16594	3	NAN	NAN	NAN	NAN	23.15	23.41	NAN	NAN	NAN	NAN	NAN	NAN
TAP1	Q03518	9	25.31	25.52	25.21	24.39	24.49	24.37	25.01	23.91	24.47	24.47	24.11	23.70
TAP2	Q03519	6	25.21	24.82	24.79	24.19	23.95	23.92	24.65	22.80	NAN	22.94	22.93	23.71
TAPBP	O15533	3	NAN	NAN	NAN	NAN	23.62	23.80	NAN	NAN	NAN	NAN	NAN	NAN
TARS	P26639	8	23.85	24.59	NAN	24.46	24.63	24.64	NAN	NAN	NAN	NAN	NAN	NAN
TBC1D15	Q8TC07	7	NAN	23.70	NAN	NAN	23.47	23.62	23.27	23.11	NAN	NAN	NAN	NAN
TBC1D9B	Q66K14	4	NAN	24.37	NAN	NAN	22.24	NAN	NAN	NAN	NAN	NAN	NAN	NAN
TBCB	Q99426	4	NAN	NAN	NAN	NAN	23.18	22.98	NAN	NAN	NAN	NAN	NAN	NAN
TBCD	Q9BTW9	5	NAN	NAN	NAN	NAN	22.67	22.45	NAN	NAN	NAN	NAN	NAN	NAN
TBK1	Q9UHD2	3	NAN	23.67	NAN	NAN	22.24	22.32	NAN	NAN	NAN	NAN	NAN	NAN
TBL2	Q9Y4P3	30	25.87	26.51	26.72	27.05	26.93	26.81	29.20	28.44	28.82	29.24	29.27	28.73
TBL3	Q12788	11	NAN	NAN	NAN	NAN	NAN	NAN	25.97	24.61	25.34	24.67	25.49	24.59
TBRG4	Q969Z0	6	NAN	24.67	NAN	NAN	23.24	NAN	NAN	NAN	NAN	NAN	NAN	NAN
TCEB1	Q15369	3	22.71	23.00	22.92	24.32	23.55	24.52	NAN	NAN	NAN	NAN	NAN	NAN
TCEB2	Q15370	4	NAN	NAN	NAN	NAN	NAN	NAN	23.12	23.45	23.38	NAN	23.27	23.11
TCERG1	O14776	6	NAN	23.56	NAN	NAN	24.02	23.98	23.36	NAN	23.15	NAN	NAN	NAN
TCF25	Q9BQ70	12	NAN	23.10	NAN	NAN	23.37	23.31	24.61	24.52	24.50	24.13	24.00	23.85
TCIRG1	Q13488	20	22.44	26.28	23.72	NAN	22.26	NAN	26.21	26.95	25.71	27.14	27.30	26.74
TCP1	P17987	35	30.48	30.39	30.78	30.74	30.95	30.97	28.41	29.51	28.72	29.42	28.98	29.29
TECR	Q9NZ01	11	26.06	25.36	26.44	26.43	26.17	26.32	24.02	24.44	24.33	24.70	23.96	23.99
TEX10	Q9NXF1	9	NAN	NAN	NAN	NAN	NAN	NAN	26.45	25.37	26.48	25.57	26.16	25.51
TFB1M	Q8WVM0	6	NAN	NAN	NAN	NAN	NAN	NAN	25.14	23.51	24.62	23.77	NAN	23.78
TFG	Q92734	8	NAN	NAN	24.84	25.77	25.89	25.76	24.96	24.72	24.20	NAN	NAN	NAN
TFRC	P02786	31	28.03	29.29	28.23	28.88	28.80	28.80	27.16	27.40	26.98	28.12	27.61	28.24
TGM2	P21980	20	25.01	28.27	26.38	NAN	NAN	22.83	28.22	26.48	27.73	26.70	27.72	26.66
TGOLN2	O43493	4	21.74	NAN	22.27	NAN	NAN	NAN	NAN	NAN	NAN	22.23	NAN	22.07
THEX1	Q8IV48	7	NAN	NAN	NAN	NAN	NAN	NAN	25.26	23.81	24.04	23.89	23.85	23.64
THUMPD1	Q9NXG2	4	NAN	NAN	NAN	NAN	23.02	23.20	23.09	23.77	23.17	23.60	23.76	24.23
THY1	P04216	4	27.33	28.07	27.15	26.55	26.70	26.25	29.95	29.88	29.77	30.30	29.90	30.10
TIAL1	Q01085	4	24.22	23.39	24.23	24.55	24.70	24.65	NAN	NAN	NAN	23.62	NAN	23.18
TIMM13	Q9Y5L4	3	NAN	NAN	NAN	NAN	25.11	24.41	NAN	NAN	NAN	NAN	NAN	NAN
TIMM23	O14925	4	24.44	NAN	24.64	24.50	24.51	25.10	NAN	NAN	NAN	NAN	NAN	NAN
TIMM44	O43615	8	27.40	27.66	27.74	28.18	28.67	28.67	24.19	26.98	25.82	26.58	26.67	27.76
TIMM50	Q3ZCQ8	10	26.56	25.95	26.90	27.39	27.38	27.77	24.75	24.63	24.45	25.36	24.80	25.50
TIPRL	O75663	6	24.25	23.20	25.45	24.71	24.24	24.59	NAN	NAN	NAN	NAN	NAN	NAN
TJP2	Q9UDY2	8	NAN	NAN	NAN	NAN	NAN	NAN	23.85	23.97	23.84	NAN	NAN	NAN

TKT	Q16832	20	26.05	27.17	26.53	27.87	27.91	27.67	25.17	26.42	26.35	26.84	26.81	27.59
TLDC1	Q6P9B6	5	23.37	24.79	24.27	24.28	24.50	24.46	25.08	24.97	NAN	23.91	24.03	25.19
TM9SF1	O15321	4	23.40	23.36	24.39	24.55	23.60	24.12	NAN	NAN	NAN	NAN	NAN	NAN
TM9SF2	Q99805	7	25.02	24.79	25.46	26.02	24.83	25.34	NAN	NAN	NAN	NAN	NAN	NAN
TM9SF4	Q92544	5	23.92	23.31	24.09	25.43	24.72	25.06	NAN	NAN	NAN	NAN	NAN	NAN
TMA16	Q96EY4	3	NAN	NAN	NAN	NAN	NAN	NAN	24.54	23.81	24.76	NAN	NAN	NAN
TMBIM1	Q969X1	2	NAN	21.86	NAN	NAN	NAN	23.13	NAN	NAN	NAN	NAN	NAN	NAN
TMCO1	Q9UM00	3	26.45	25.40	26.95	25.85	25.25	25.67	25.26	24.67	25.47	25.06	24.87	25.04
TMED4	Q7Z7H5	6	23.79	23.27	24.21	24.61	24.07	24.06	NAN	NAN	NAN	NAN	NAN	NAN
TMED5	Q9Y3A6	3	NAN	24.49	NAN	NAN	22.35	22.55	NAN	NAN	NAN	NAN	NAN	NAN
TMED7	Q9Y3B3	8	26.41	25.43	27.06	27.48	27.05	27.20	25.04	25.13	24.58	26.17	25.61	26.16
TMEM113	Q6UXN9	3	NAN	NAN	NAN	NAN	NAN	NAN	22.91	23.30	23.26	NAN	NAN	NAN
TMEM147	Q9BVK8	2	NAN	22.09	NAN	NAN	22.75	NAN	NAN	NAN	NAN	NAN	NAN	NAN
TMEM165	Q9HC07	6	25.38	24.68	25.70	26.62	25.83	26.13	23.41	23.51	24.05	23.31	24.16	23.31
TMEM16K	Q9NW15	7	23.20	23.80	23.53	NAN	23.05	NAN	NAN	NAN	NAN	NAN	NAN	NAN
TMEM214	Q6NUQ4	9	NAN	23.50	NAN	NAN	23.95	NAN	23.79	24.18	24.07	24.31	24.13	NAN
TMEM259	Q4ZIN3	3	NAN	21.98	NAN	NAN	NAN	22.45	NAN	NAN	NAN	NAN	NAN	NAN
TMEM33	P57088	10	27.08	27.17	27.24	27.45	27.27	27.46	25.96	26.23	25.78	25.85	25.68	26.17
TMEM43	Q9BTV4	29	28.28	29.36	28.62	26.38	25.92	26.37	30.49	30.20	30.35	30.10	30.06	30.16
TMPO	P42166	8	23.80	24.30	24.58	25.76	25.08	24.67	24.08	24.50	25.23	24.87	24.79	24.47
TMTC3	Q6ZXV5	7	24.71	24.50	25.01	24.23	24.25	24.44	NAN	NAN	NAN	NAN	NAN	NAN
TMX1	Q9H3N1	7	25.13	24.82	25.76	25.50	25.57	25.58	23.32	24.11	23.85	24.60	24.81	25.04
TMX2	Q9Y320	3	24.28	24.52	25.15	21.87	21.67	21.98	23.57	22.96	23.36	22.48	22.67	22.14
TMX3	Q96JJ7	19	27.90	26.79	28.53	28.82	28.63	28.86	24.54	25.73	25.55	26.71	25.85	26.19
TMX4	Q9H1E5	4	23.86	NAN	25.08	24.78	24.81	24.53	NAN	NAN	NAN	23.63	NAN	23.98
TNPO2	O14787	17	NAN	26.42	NAN	NAN	22.90	24.87	NAN	NAN	NAN	NAN	NAN	NAN
TNPO3	Q9Y5L0	7	23.15	26.43	NAN	22.32	22.77	22.96	NAN	NAN	NAN	21.78	21.57	21.54
TOE1	Q96GM8	4	NAN	NAN	NAN	NAN	NAN	NAN	25.32	NAN	24.21	23.31	23.79	NAN
TOLLIP	Q9H0E2	3	23.61	24.22	23.74	23.73	23.59	23.70	24.71	23.55	23.99	24.16	25.10	23.90
TOM1	O60784	7	NAN	NAN	23.73	22.77	NAN	NAN	24.00	23.87	24.42	23.82	24.42	23.92
TOM1L2	Q6ZVM7	7	NAN	NAN	NAN	NAN	NAN	NAN	24.57	23.98	25.30	23.70	25.45	24.29
TOMM22	Q9NS69	6	23.89	25.42	24.59	25.46	24.82	24.92	24.97	25.92	NAN	24.07	24.92	24.76
TOMM40	O96008	13	25.81	26.73	26.07	25.81	25.41	25.53	26.93	26.94	26.79	25.66	26.55	26.52
TOMM70A	O94826	12	23.33	26.26	23.54	27.08	26.63	26.81	23.78	23.90	23.73	24.41	24.08	24.72
TOP2A	P11388	31	NAN	NAN	NAN	NAN	NAN	NAN	28.08	25.56	26.25	25.63	26.11	25.11
TOR1A	O14656	5	23.22	23.30	25.12	23.74	23.76	23.83	NAN	22.06	21.97	23.16	22.29	23.22
TOR1AIP1	Q5JTV8	9	24.39	24.45	24.60	25.67	25.10	25.64	23.09	NAN	24.08	24.51	24.17	24.38
TOR1AIP2	Q8NFQ8	3	NAN	23.31	NAN	NAN	24.03	23.69	NAN	NAN	NAN	21.71	22.85	22.60
TP53	P04637	5	26.32	24.58	26.88	25.31	24.08	24.51	NAN	NAN	NAN	NAN	NAN	NAN
TPM1	P09493	41	NAN	NAN	NAN	NAN	NAN	NAN	24.11	23.73	24.27	23.82	23.92	23.71
TPM1	P09493	43	NAN	NAN	NAN	NAN	NAN	NAN	24.71	NAN	24.64	28.63	27.90	28.92
TPM2	P07951	50	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	24.48	NAN	25.58
TPP1	O14773	7	25.94	26.39	26.60	27.62	27.24	27.39	25.27	25.81	25.28	26.15	25.69	26.17
TPP2	P29144	13	24.69	25.12	24.65	25.06	24.78	24.51	NAN	NAN	NAN	24.06	24.49	24.47
TRA2B	P62995	8	NAN	NAN	NAN	NAN	NAN	NAN	24.11	23.86	24.19	24.63	24.42	23.69
TRAP1	Q12931	17	23.72	25.14	23.57	26.86	26.50	26.63	NAN	23.03	23.30	NAN	22.62	23.11
TRAPPC3	O43617	4	NAN	NAN	22.79	22.98	23.24	23.29	NAN	22.23	22.61	NAN	NAN	NAN
TRAPPC5	Q8IUR0	4	NAN	23.32	NAN	NAN	23.25	23.43	NAN	NAN	NAN	NAN	NAN	NAN
TRIM22	Q8IYM9	6	NAN	NAN	NAN	NAN	NAN	NAN	23.42	23.84	24.40	NAN	22.49	22.21
TRIM28	Q13263	37	27.63	28.35	28.01	28.63	28.34	28.55	27.61	27.60	27.46	28.12	27.70	27.84
TRIM32	Q13049	7	24.00	24.91	23.80	24.06	24.19	24.04	25.12	NAN	24.47	NAN	NAN	NAN
TRIM56	Q9BRZ2	14	NAN	NAN	NAN	NAN	NAN	NAN	28.34	26.95	27.45	26.01	27.06	26.08
TRIO	O75962	12	NAN	24.61	NAN	NAN	23.31	23.92	24.33	23.98	24.02	NAN	NAN	NAN
TRIP12	Q14669	19	25.76	26.25	23.69	24.77	25.04	24.65	26.63	24.88	25.84	25.27	25.66	25.61
TRIP13	Q15645	6	NAN	23.97	NAN	NAN	23.97	24.43	23.58	23.43	23.71	NAN	23.66	23.72
TRIP4	Q15650	6	NAN	NAN	NAN	NAN	NAN	NAN	24.53	22.73	24.30	23.68	23.83	23.71
TRMT10C	Q7L0Y3	22	28.06	26.87	25.99	27.48	27.42	27.64	27.99	27.19	27.86	26.48	27.10	26.70
TRMT112	Q9UI30	3	NAN	23.98	NAN	NAN	23.98	24.04	NAN	NAN	NAN	NAN	NAN	NAN
TRMT1L	Q7Z2T5	6	NAN	NAN	NAN	NAN	NAN	NAN	25.06	23.45	24.79	23.47	22.90	22.86
TROVE2	P10155	12	25.00	24.75	24.97	24.56	24.72	24.89	25.65	25.70	26.07	25.10	25.67	25.60
TRPM2	O94759	33	NAN	NAN	NAN	NAN	23.21	22.18	NAN	NAN	NAN	NAN	NAN	NAN
TRPT1	Q86TN4	2	NAN	NAN	NAN	NAN	NAN	NAN	22.65	22.84	23.16	NAN	NAN	NAN
TSG101	Q99816	7	NAN	NAN	NAN	NAN	23.94	23.97	23.54	24.36	23.67	23.68	23.96	24.03
TSPYL1	Q9H0U9	4	NAN	NAN	NAN	NAN	NAN	NAN	23.18	22.22	22.42	NAN	NAN	NAN
TSR1	Q2NL82	28	22.45	25.57	24.03	24.07	24.95	24.90	28.87	28.30	28.79	27.81	28.47	27.67
TTC37	Q6PGP7	52	22.72	24.97	21.78	NAN	24.40	22.53	28.95	29.23	28.90	27.91	28.53	28.14
TTLL12	Q14166	9	NAN	25.40	23.51	24.51	24.56	24.62	NAN	NAN	NAN	23.64	NAN	23.88
TTN	Q8WZ42	4	23.68	NAN	23.09	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN	NAN
TUBA4A	P68366	32	26.26	26.52	26.46	26.52	26.31	26.52	24.31	24.07	25.12	24.98	25.12	24.93
TUBB8	Q3ZCM7	12	30.80	31.92	30.36	29.74	29.77	29.97	29.28	29.72	29.65	27.73	27.44	28.75
TUBG2	Q9NRH3	6	23.87	24.21	24.04	24.39	25.05	24.86	24.65	24.04	23.63	NAN	NAN	NAN
TUFM	P49411	28	28.33	28.77	28.85	29.81	29.55	29.76	28.13	28.15	27.98	28.78	28.11	28.28
TXLNA	P40222	9	23.53	24.22	24.10	24.30	24.41	24.48	23.82	24.22	23.75	NAN	NAN	NAN
TXNDC12	O95881	2	22.39	NAN	22.80	23.63	22.74	23.15	NAN	NAN	NAN	NAN	NAN	NAN
TXNDC9	O14530	2	NAN	22.40	NAN	NAN	23.45	23.20	NAN	NAN	NAN	NAN	NAN	NAN
TXNL1	O43396	12	24.73	25.41	24.17	26.77	26.87	26.85	24.48	24.92	24.58	24.86	25.28	25.35
U2AF1	Q01081	15	25.48	27.53	26.62	26.66	26.79	26.35	29.68	28.78	29.40	28.70	29.34	28.69
U2AF2	P26368	22	23.69	28.69	25.39	28.12	28.41	27.52	31.57	30.38	31.30	29.67	30.88	30.26
U2SURP	O15042	8	NAN	NAN	NAN	NAN	NAN	NAN	24.81	24.75	24.58	24.67	24.75	24.35
UACA	Q9BZF9	11	NAN	NAN	NAN	NAN	NAN	NAN	25.25	24.79	25.21	23.52	24.98	24.29
UAP1	Q16222	5	22.90	25.33	23.25	23.52	24.45	23.64	22.44	NAN	23.10	NAN	22.73	23.56
UBA2	Q9UBT2	2	NAN	NAN	NAN	NAN	22.91	23.03	NAN	NAN	NAN	NAN	NAN	NAN
UBAP2L	Q14157	10	24.48	24.60	24.30	24.48	24.30	23.73	25.47	25.20	24.76	25.27	25.48	25.45
UBE2D2	P62837	3	24.48	25.31	NAN	24.66	24.63	24.85	24.02	23.14	NAN	NAN	NAN	NAN
UBE2I	P63279	3	NAN	23.36	NAN	NAN	23.47	23.79	NAN	NAN	NAN	NAN	NAN	NAN

UBE2N	P61088	4	NAN	23.06	NAN	NAN	23.19	22.86	NAN	NAN	NAN	NAN	NAN	NAN
UBE3A	Q05086	4	NAN	NAN	NAN	NAN	23.46	24.02	NAN	NAN	NAN	NAN	NAN	NAN
UBE3C	Q15386	12	23.59	25.79	24.29	24.30	24.14	24.43	22.26	22.71	22.78	23.91	22.80	NAN
UBTF	P17480	12	NAN	22.72	NAN	NAN	23.55	NAN	26.86	25.54	25.96	25.55	26.07	24.80
UBXN4	Q92575	4	NAN	24.43	NAN	NAN	24.98	NAN	NAN	NAN	NAN	23.97	NAN	24.16
UCHL1	P09936	4	NAN	NAN	NAN	NAN	24.52	25.36	NAN	24.45	24.22	NAN	24.69	24.62
UCK2	Q9BZX2	5	23.08	25.39	NAN	24.27	24.23	25.00	24.24	24.13	NAN	NAN	NAN	NAN
UFD1L	Q92890	4	22.47	22.51	NAN	25.38	24.71	25.36	NAN	NAN	NAN	NAN	NAN	NAN
UFL1	O94874	27	25.41	27.07	24.20	27.06	27.00	27.06	27.45	28.04	28.50	27.76	27.59	28.14
UFSP2	Q9NUQ7	5	NAN	23.62	NAN	NAN	23.94	24.18	NAN	NAN	NAN	NAN	NAN	NAN
UGGT1	Q9NYU2	74	29.52	29.92	28.69	30.41	30.28	30.29	28.81	29.06	28.63	29.51	29.21	29.81
UGP2	Q16851	8	24.99	25.05	24.56	25.26	25.97	25.66	24.28	24.41	24.68	24.50	24.73	25.59
UHRF1	Q96T88	3	NAN	NAN	NAN	NAN	NAN	NAN	22.68	22.44	22.18	22.32	22.48	22.41
UMPS	P11172	10	23.81	26.42	NAN	24.02	23.98	24.69	23.73	23.98	23.87	23.85	NAN	24.80
UPF1	Q92900	34	25.76	26.91	25.71	26.69	27.00	26.93	26.62	26.60	26.27	26.92	26.84	27.04
UQCRFS1	P47985	7	25.49	23.94	25.03	25.77	25.56	25.45	24.28	25.11	24.98	24.99	23.88	25.52
UQCRQ	O14949	3	23.48	21.87	23.75	23.84	23.44	23.42	NAN	NAN	NAN	NAN	NAN	NAN
URB1	O60287	34	NAN	NAN	NAN	NAN	NAN	NAN	27.80	26.32	27.99	25.88	26.98	25.34
URB2	Q14146	18	NAN	NAN	NAN	NAN	NAN	NAN	27.63	26.05	26.86	25.58	26.67	25.59
UROD	P06132	14	23.40	23.88	25.22	27.23	27.24	27.12	NAN	NAN	NAN	23.69	NAN	24.36
USMG5	Q96IX5	3	NAN	NAN	NAN	NAN	23.91	23.98	NAN	NAN	NAN	NAN	NAN	NAN
USP11	P51784	11	NAN	NAN	23.93	25.56	25.22	26.04	NAN	NAN	NAN	23.25	NAN	22.39
USP14	P54578	5	NAN	24.48	NAN	NAN	24.52	24.34	NAN	NAN	NAN	NAN	NAN	NAN
USP24	Q9UPU5	2	NAN	22.17	NAN	NAN	22.83	NAN	NAN	NAN	NAN	NAN	NAN	NAN
USP47	Q96K76	6	23.22	23.12	NAN	22.79	23.02	23.38	NAN	NAN	NAN	NAN	NAN	NAN
USP5	P45974	22	24.57	26.21	25.05	26.10	26.34	26.56	23.07	24.07	23.81	24.56	24.42	25.32
UTP18	Q9Y5J1	4	NAN	NAN	NAN	NAN	NAN	NAN	23.73	22.93	23.60	NAN	NAN	NAN
UTP20	O75691	29	NAN	NAN	NAN	NAN	NAN	NAN	27.62	25.73	26.55	24.59	25.77	23.11
UTP23	Q9BRU9	2	NAN	NAN	NAN	NAN	NAN	NAN	23.97	NAN	23.79	NAN	NAN	NAN
UTP3	Q9NQZ2	7	23.45	25.84	23.11	22.57	22.81	22.78	25.64	24.38	24.17	22.61	23.65	23.13
VAC14	Q08AM6	6	25.16	24.51	25.62	24.04	23.56	23.44	NAN	NAN	NAN	NAN	NAN	NAN
VAMP2	P63027	3	NAN	23.44	NAN	NAN	24.48	24.10	NAN	NAN	NAN	NAN	NAN	NAN
VAT1	P54219	15	25.18	26.71	25.25	26.36	26.81	26.87	22.89	25.24	25.35	25.40	25.19	26.05
VBP1	P61758	2	NAN	NAN	NAN	NAN	NAN	NAN	NAN	22.94	23.30	NAN	NAN	NAN
VDAC1	P21796	22	28.32	29.57	28.71	29.41	29.27	29.07	29.40	29.31	29.17	29.74	29.49	29.78
VDAC2	P45880	17	28.32	28.99	28.68	28.56	28.25	28.23	29.03	28.96	28.68	29.41	29.39	29.32
VDAC3	Q9Y277	13	25.93	27.25	26.52	26.65	26.34	26.49	27.65	27.34	27.09	27.55	27.56	27.69
VPS16	Q9H269	8	25.66	25.26	24.00	24.81	24.56	24.77	NAN	NAN	NAN	NAN	NAN	NAN
VPS18	Q9P253	12	24.71	25.36	24.73	25.86	25.19	24.90	23.43	23.08	NAN	23.99	23.83	23.54
VPS26A	O75436	7	23.83	NAN	NAN	24.73	24.60	24.56	NAN	NAN	NAN	23.80	24.09	23.93
VPS29	Q9UBQ0	5	NAN	NAN	NAN	NAN	24.56	24.15	NAN	NAN	NAN	NAN	NAN	NAN
VPS33A	Q96AX1	10	25.57	25.59	25.33	23.98	23.93	24.13	22.75	22.55	23.18	NAN	NAN	NAN
VPS41	P49754	5	24.11	NAN	24.02	23.36	23.45	23.33	NAN	NAN	NAN	NAN	NAN	NAN
VPS4B	O75351	5	23.27	24.69	23.85	24.22	24.27	24.13	23.45	NAN	23.49	23.34	23.97	NAN
VPS53	Q5VIR6	3	22.98	24.41	NAN	22.91	22.57	22.42	NAN	NAN	NAN	NAN	NAN	NAN
VTA1	Q9NP79	2	NAN	NAN	NAN	NAN	24.29	24.02	23.98	23.87	23.65	23.98	24.40	24.91
VTI1B	Q9UEU0	4	NAN	NAN	NAN	NAN	22.61	22.53	22.30	22.79	21.64	NAN	NAN	NAN
WARS	P23381	21	27.25	26.56	27.04	27.15	27.81	27.54	24.62	25.65	26.06	25.80	26.31	26.26
WASH4P	A8MWX3	2	NAN	NAN	NAN	NAN	23.70	23.19	NAN	NAN	NAN	NAN	NAN	NAN
WDR12	Q9GZL7	6	NAN	23.77	NAN	NAN	NAN	23.26	24.77	23.36	24.78	NAN	23.52	23.46
WDR18	Q9BV38	6	NAN	NAN	NAN	NAN	NAN	NAN	25.27	23.57	24.50	23.08	23.73	23.49
WDR3	Q9UNX4	14	NAN	NAN	NAN	NAN	NAN	NAN	25.77	24.60	25.52	25.17	24.96	24.74
WDR36	Q8NI36	11	NAN	23.33	NAN	NAN	NAN	23.43	25.66	23.97	24.73	24.14	25.31	NAN
WDR47	O94967	2	NAN	NAN	NAN	NAN	22.60	22.43	NAN	NAN	NAN	NAN	NAN	NAN
WDR6	Q9NNW5	4	NAN	NAN	NAN	NAN	23.56	23.41	23.32	23.32	23.95	NAN	NAN	NAN
WDR61	Q9GZS3	12	25.75	25.72	26.11	26.12	25.95	25.72	26.55	27.00	26.73	26.50	26.89	27.00
WFS1	O76024	3	NAN	NAN	22.76	22.66	22.52	22.69	NAN	NAN	NAN	NAN	NAN	NAN
WRN	Q14191	2	NAN	NAN	NAN	NAN	NAN	NAN	21.52	20.86	21.37	NAN	NAN	NAN
WRNIP1	Q96S55	6	23.78	23.30	23.46	24.13	23.68	23.62	NAN	NAN	NAN	NAN	NAN	NAN
XPO1	O14980	35	26.89	28.01	27.32	27.75	27.72	27.98	26.02	26.39	26.90	26.35	26.44	26.49
XPO5	Q9HAV4	21	24.47	27.07	25.37	24.93	24.70	25.58	NAN	NAN	NAN	22.48	22.91	22.68
XPOT	O43592	16	25.91	27.25	25.65	25.96	26.23	26.35	24.42	23.84	24.81	23.97	24.04	24.45
XRCC5	P13010	44	29.83	29.95	28.10	29.48	29.44	29.30	27.52	27.90	28.14	28.24	27.73	28.00
XRCC6	P12956	36	29.44	29.52	27.57	29.19	29.20	29.11	27.46	27.49	28.22	28.00	27.58	27.98
XRN2	Q9H0D6	11	24.68	24.00	24.11	25.00	25.10	25.05	24.71	24.40	24.67	25.23	25.44	25.04
YARS	P54577	15	23.97	26.75	23.71	23.96	24.95	24.28	22.73	NAN	23.95	23.51	24.48	24.72
YES1	P07947	8	23.96	25.12	23.35	24.15	NAN	24.30	24.16	NAN	23.81	NAN	NAN	NAN
YIF1A	O95070	4	NAN	24.30	NAN	NAN	NAN	24.16	NAN	NAN	NAN	NAN	NAN	NAN
YIF1B	Q5BJH7	3	NAN	NAN	NAN	NAN	23.63	23.76	NAN	NAN	NAN	NAN	NAN	NAN
YME1L1	Q96TA2	12	23.96	25.20	24.49	25.75	25.73	25.56	25.44	23.58	24.00	NAN	24.70	24.36
YTHDC2	Q9H6S0	11	NAN	NAN	NAN	NAN	NAN	NAN	26.67	24.75	25.49	23.44	24.76	22.69
YTHDF1	Q9BYJ9	5	NAN	NAN	NAN	NAN	NAN	NAN	24.08	NAN	22.90	NAN	22.82	22.75
YTHDF2	Q9Y5A9	7	23.00	23.42	NAN	23.31	23.94	23.32	24.03	23.63	23.74	23.76	24.36	23.56
YTHDF3	Q7Z739	5	NAN	NAN	NAN	NAN	NAN	NAN	24.05	23.48	23.60	23.29	23.58	23.48
ZC3H18	Q86VM9	3	NAN	NAN	NAN	NAN	NAN	NAN	22.20	NAN	21.82	NAN	NAN	NAN
ZC3H4	Q9UPT8	4	NAN	NAN	NAN	NAN	NAN	NAN	24.07	23.03	23.17	NAN	NAN	NAN
ZC3H7A	Q8IWR0	11	NAN	NAN	NAN	NAN	NAN	NAN	24.87	24.52	24.74	24.45	24.56	24.27
ZC3H7B	Q9UGR2	10	NAN	NAN	NAN	NAN	NAN	NAN	24.18	24.28	24.14	NAN	23.98	23.86
ZC3HAV1	Q7Z2W4	29	22.94	25.22	22.91	22.95	23.84	24.33	27.94	27.15	27.19	27.37	27.66	26.59
ZFPL1	O95159	2	NAN	NAN	NAN	NAN	22.94	23.03	NAN	NAN	NAN	NAN	NAN	NAN
ZFR	Q96KR1	15	NAN	23.94	NAN	NAN	24.86	24.15	26.46	25.60	26.30	25.48	26.30	25.35
ZMPSTE24	O75844	8	23.81	24.97	22.80	24.86	24.89	24.69	NAN	NAN	NAN	23.51	22.54	23.62
ZNF622	Q969S3	23	NAN	NAN	NAN	NAN	NAN	NAN	27.75	25.72	27.76	26.76	25.96	26.26